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(71) Applicant (*for all designated States except US*): **3M INNOVATIVE PROPERTIES COMPANY** [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **KSHIRSAGAR, Tushar A.**, [IN/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **MERRILL, Bryon A.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **LANGER, Scott E.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **LINDSTROM, Kyle J.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **JOHANNESSEN, Sarah C.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **MARSZALEK, Gregory J.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **WURST, Joshua R.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **MANSKE, Karl J.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **NIWAS, Shri**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **LUNDQUIST, Gregory D. Jr.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **HEPPNER, Philip D.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **GRIESGRABER, George W.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US). **DANIELSON, Michael E.**, [US/US]; 3m Center, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

(74) Agents: **ERSFELD, Dean A.**, et al.; 3m Center, Office Of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, Minnesota 55133-3427 (US).

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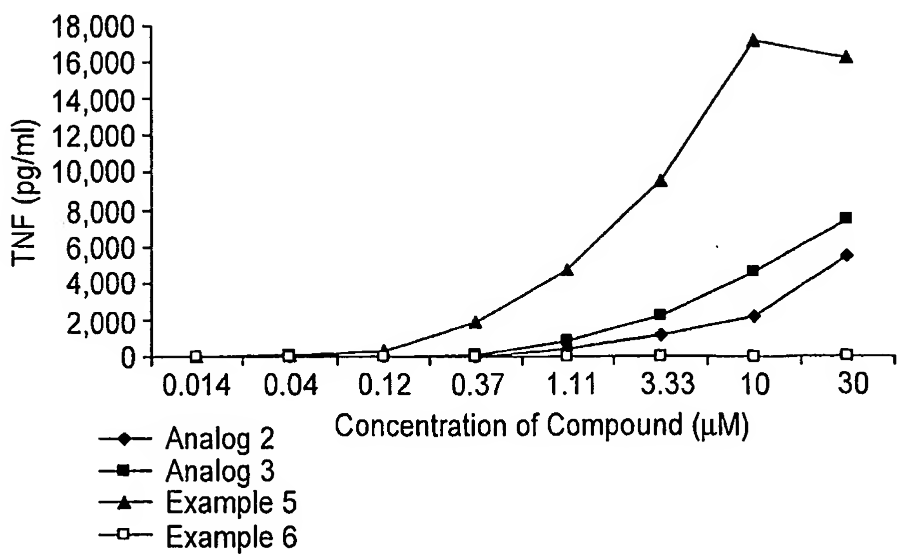
(54) Title: METHOD OF PREFERENTIALLY INDUCING THE BIOSYNTHESIS OF INTERFERON



(57) Abstract: A method of preferentially inducing IFN-α biosynthesis in an animal comprising administering certain imidazo[4,5-c] ring compounds with a hydroxymethyl or hydroxyethyl substituent at the 2-position or pharmaceutical compositions containing the compounds, intermediates, methods of making, and methods of using these compounds a immunomodulators for treatment of diseases including viral and neoplastic diseases comprising preferentially inducing IFN-α biosynthesis in an animal are disclosed.

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METHOD OF PREFERENTIALLY INDUCING THE BIOSYNTHESIS OF INTERFERON

CROSS REFERENCE TO RELATED APPLICATIONS

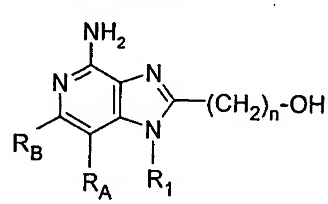
The present invention claims priority to U.S. Provisional Application Serial Nos. 60/655452, 60/655508, 60/655380, and 60/655495, each of which was filed on February 23, 2005, and each of which is incorporated herein by reference.

BACKGROUND

Certain compounds have been found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders. However, there continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other means.

SUMMARY

The present invention provides a method of preferentially inducing the biosynthesis of interferon (α) (IFN-α) in an animal comprising administering an effective amount of a compound of Formulas I, II, and/or III:



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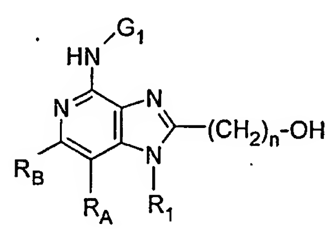
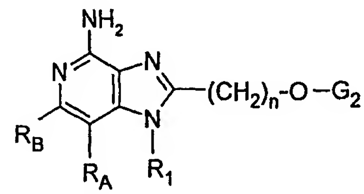


II



III

wherein R_A, R_B, R_1, G_1, G_2, and n are as defined below.

It has now surprisingly been discovered that the amount of TNF-α induced by the 2-(hydroxyalkyl) substituted compounds of Formula I is substantially less than the amount of TNF-α induced by closely related analogs having an alkyl or alkyl ether substituent at the 2-position and that the compounds of Formula I, which can be administered as Formula I, Formula II, and/or Formula III, and/or a pharmaceutically acceptable salt thereof, can still retain the ability to induce the biosynthesis of IFN-α. See, for example, Figures 1 -8 below. The reduction in the amount of TNF-α induced is seen over a broad range of test concentrations. In some embodiments the amount of TNF-α induced by the compounds of Formulas I, II, and/or III is at least two-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position. In other embodiments the amount of TNF-α induced by the compounds of Formulas I, II, and/or III is at least three-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position. In still other embodiments the amount of TNF-α induced by the compounds of Formulas I, II, and/or III is at least four-fold less than the amount of TNF-α induced by analogs having an alkyl or alkyl ether substituent at the 2-position.

The compounds or salts of Formulas I, II, and III are especially useful as immune response modifiers due to their ability to preferentially induce interferon-α, thus providing a benefit over compounds that also induce pro-inflammatory cytokines (e.g. TNF-α) or that induce pro-inflammatory cytokines at higher levels.

A compound is said to preferentially induce IFN-α if, when tested according to the test methods described herein, the effective minimum concentration for IFN-α induction is less than the effective minimum concentration for TNF-α induction. In some embodiments, the effective minimum concentration for IFN-α induction is at least 3-fold less than the effective minimum concentration for TNF-α induction. In some embodiments, the effective minimum concentration for IFN-α induction is at least 6-fold

less than the effective minimum concentration for TNF-α induction. In other embodiments, the effective minimum concentration for IFN-α induction is at least 9-fold less than the effective minimum concentration for TNF-α induction. In some embodiments, when tested according to the test methods described herein, the amount TNF-α induced by compounds of Formulas I, II, and/or III is at or below the background level of TNF-α in the test method.

The invention further provides a method of preferentially inducing the biosynthesis of IFN-α in an animal wherein an effective amount of the compound or salt of Formulas I, II, and/or III (or any one of the embodiments described herein) is administered as a pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of Formulas I, II, and/or III (or any one of the embodiments described herein) and a pharmaceutically acceptable carrier.

The invention further provides a method of treating a viral infection or disease and/or treating a neoplastic disease in an animal comprising preferentially inducing the biosynthesis of IFN-α in the animal by administering an effective amount of a compound or salt of Formulas I, II, and/or III (or any one of the embodiments described herein) or a pharmaceutical composition containing an effective amount of a compound or salt of Formulas I, II, and/or III (or any one of the embodiments described herein) to the animal.

In addition, methods of synthesizing compounds of Formulas I, II, and III and intermediates useful in the synthesis of these compounds are provided.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the IFN-α dose response curves (corresponding to values shown in Table 7 below) for Example 6, Analog 2, Analog 3, and Analog 5.

Figure 2 shows the TNF-α dose response curves (corresponding to values shown in Table 7 below) for Example 6, Analog 2, Analog 3, and Analog 5.

Figure 3 shows the IFN-α dose response curves (corresponding to values shown in Table 7 below) for Example 7, Analog 1, Analog 2, and Analog 4.

Figure 4 shows the TNF-α dose response curves (corresponding to values shown in Table 7 below) for Example 7, Analog 1, Analog 2, and Analog 4.

Figure 5 shows the IFN-α dose response curves (corresponding to values shown in Table 8 below) for Example 148, Example 149, Analog 6, and Analog 7.

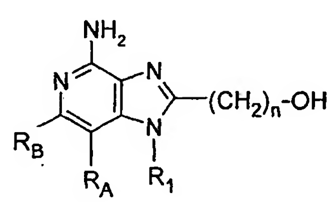
Figure 6 shows the TNF-α dose response curves (corresponding to values shown in Table 8 below) for Example 148, Example 149, Analog 6, and Analog 7.

Figure 7 shows the IFN-α dose response curves (corresponding to values shown in Table 9 below) for Example 163, Analog 8, Analog 9, and Analog 10.

Figure 8 shows the TNF-α dose response curves (corresponding to values shown in Table 9 below) for Example 163, Analog 8, Analog 9, and Analog 10.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides a method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of Formulas I, II, and/or III:



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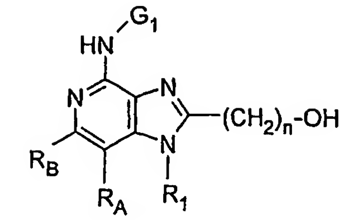

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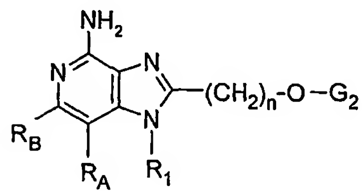
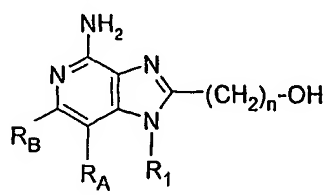


III

wherein R_A, R_B, R_1, G_1, G_2, and n are as defined below; and pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of the following Formula I:



I

wherein:

n is 1 or 2;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring

containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

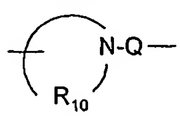
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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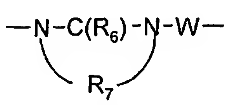

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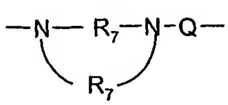

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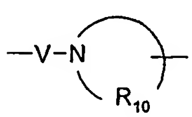

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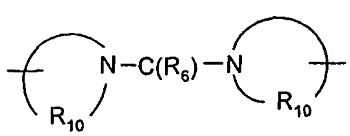


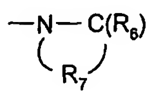
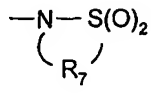
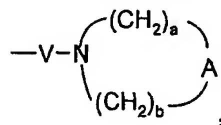
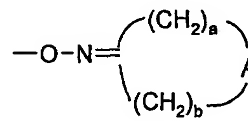
;

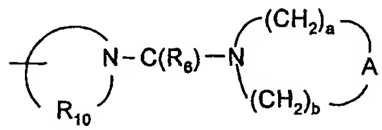
Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

 ,  ,  ,  , and

 ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

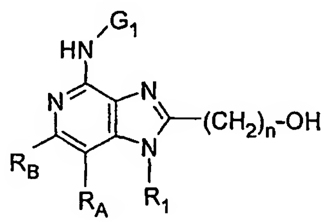
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof to the animal.

In another embodiment, the present invention provides a method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of the following Formula II, which is a prodrug:



II

wherein:

G_1 is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC_{1-4} alkyl)Y_0,

-CH_2Y_1, and

-CH(CH_3)Y_1;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –S(O)$_2$-NH_2, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl;

Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl,

amino-C_{1-4} alkylenyl, mono-N-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-N,N-C_{1-6} alkylamino-C_{1-4} alkylenyl;

Y_1 is selected from the group consisting of mono-N-C_{1-6} alkylamino, di-N,N-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl;

n is 1 or 2;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

-$N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-$N(R_9)_2$;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X-R_4,

-Z-X-Y-R_4,

-Z-X-Y-X-Y-R_4, and

-Z-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

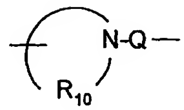
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,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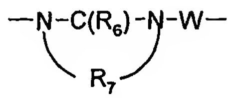
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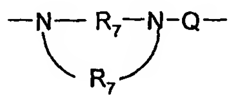
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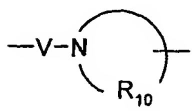
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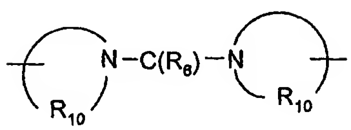
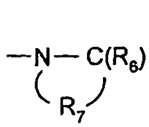

;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of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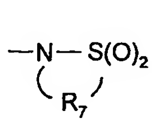
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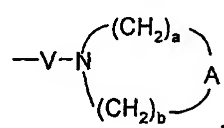
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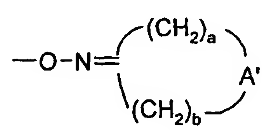
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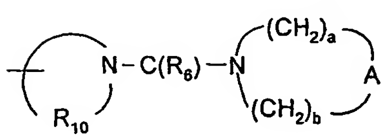

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

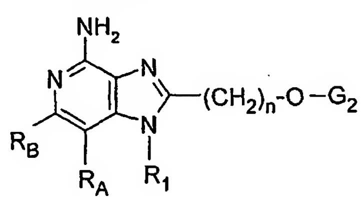
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof to the animal.

In another embodiment, the present invention provides a method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of the following Formula III, which is a prodrug:



III

wherein:

G_2 is selected from the group consisting of:

$-X_2-C(O)-R'$,

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

$-X_2-C(O)-O-R'$, and

$-C(O)-N(R'')R'$;

X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$;

$-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R'$, $-CH_2-NH-$;

R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

n is 1 or 2;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

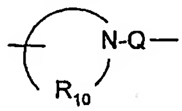
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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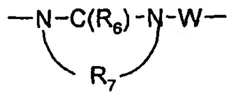

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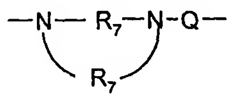

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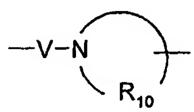

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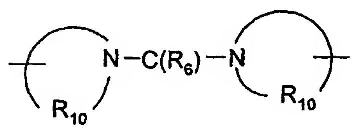
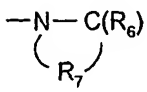
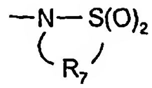
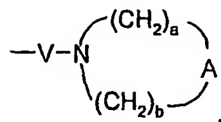
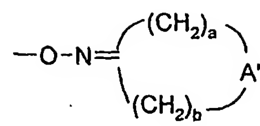


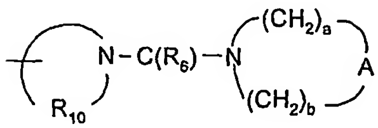
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7; or a pharmaceutically acceptable salt thereof to the animal.

As used herein "substantially less than the amount of TNF-α " means that there is at least a two-fold reduction in the maximal TNF-α response as determined using the test methods described herein.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, e.g., cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4

carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). In some embodiments, the term "heteroaryl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. In some embodiments, the term "heterocyclyl" includes a ring or ring system that contains 2-12 carbon atoms, 1-3 rings, 1-4 heteroatoms, and O, S, and N as the heteroatoms. Exemplary heterocyclyl groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, 1,1-

dioxothiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), 1,4-oxazepanyl, homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, azetidinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, 3-azabicyclo[3.2.2]non-3-yl, and the like.

The term "heterocyclyl" includes bicylic and tricyclic heterocyclic ring systems. Such ring systems include fused and/or bridged rings and spiro rings. Fused rings can include, in addition to a saturated or partially saturated ring, an aromatic ring, for example, a benzene ring. Spiro rings include two rings joined by one spiro atom and three rings joined by two spiro atoms.

When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_8)-C(O)-N(R_8)-$ each R_8 group is independently selected. In another example, when R_1 and R_3 each contain an R_4 group then each R_4 group is independently selected. In a further example, when two Y groups are present and each Y group contains one or more R_8 groups, then each Y group and each R_8 group is independently selected.

The compounds described herein can be administered according to the methods of the present invention in any of the compounds' pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the methods of the invention specifically include the use each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes

any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

The term "prodrug" means a compound that can be transformed in vivo to yield an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The prodrug, itself, may be an immune response modifying compound, including any of the salt, solvated, polymorphic, or isomeric forms described above. The transformation may occur by various mechanisms, such as through a chemical (e.g., solvolysis or hydrolysis, for example, in the blood) or enzymatic biotransformation. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For any of the compounds presented herein, each one of the following variables (e.g., X, Y, Z, R_A, R_B, R_1, R_3, R_4, R_5, Q, G_1, G_2, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables describes a compound or compounds which can be administered according to any one of the methods of the present invention, and the resulting method is an embodiment of the present invention.

For certain embodiments of any one of the above methods, n is 1.

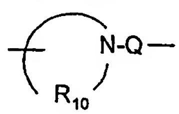
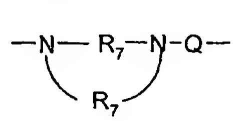
For certain embodiments of any one of the above methods, n is 2.

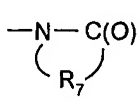
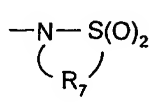
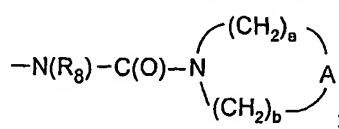
For certain embodiments of any one of the above methods, including any one of the above embodiments, R_A and R_B form a fused benzene ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group. For certain of these embodiments, the fused benzene ring is substituted by an R_3 group at the 7-position.

For certain embodiments of any one of the above methods, including any one of the above embodiments except where R_A and R_B form the fused benzene ring, R_A and R_B form a fused pyridine ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments of any one of the above methods, including any one of the above embodiments except where R_A and R_B form the fused benzene or pyridine ring, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted or substituted by one or more R groups.

For certain embodiments of any one of the above methods, including any one of the above embodiments except where R_A and R_B form the fused benzene, pyridine, or 5 to 7 membered saturated ring, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain of these embodiments, R_A and R_B are each methyl.

For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X^1-Y^1-R_4$, and $-X-R_5$; wherein X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group; Y is selected from the group consisting of -O-, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, -C(O)-, -C(O)-O-, -O-C(O)-, $-N(R_8)-Q-$, $-C(O)-N(R_8)-$, , and ; X^1 is selected from the group consisting of alkylene and arylene; Y^1 is selected from the group consisting of -S-, -C(O)-, -C(O)-O-, $-C(O)-N(R_8)-$, $-S(O)_2-N(R_8)-$, and $-N(R_8)-C(O)-$; R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo; R_5 is selected from the group consisting of:

, , and ; R_6 is selected from the group consisting of =O and =S; R_7 is C_{2-7} alkylene; R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl; R_{10} is C_{3-8} alkylene; A is selected from the group consisting of -O-,

-C(O)-, and –N(R_4)-; Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-; W is selected from the group consisting of a bond and -C(O)-; and a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, dihydroxyC_{1-4}alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one, two, or three substituents selected from the group consisting of alkyl, aryl, heteroaryl, and oxo.

For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 2-fluoro-2-methylpropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-(methylsulfonyl)ethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 2,2-dimethyl-3-(methylsulfonyl)propyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-{[(1-methylethyl)sulfonyl]amino}ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl,

2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]ethyl, , 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-methyl-2-[(ethylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-({[(1-methylethyl)amino]carbonyl}amino)ethyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, tetrahydro-2*H*-pyran-4-ylmethyl, 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

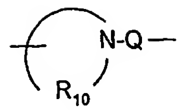
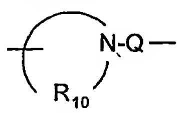
For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is selected from the group consisting of alkyl, aminoalkyl, dihydroxyalkyl, haloalkyl, and hydroxyalkyl, except where R_1 as defined does not include this definition. For certain of these embodiments, R_1 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, 2-methylpropyl, 2-amino-2-methylpropyl, 3-amino-2,2-dimethylpropyl, 2,3-dihydroxypropyl, 2-fluoro-2-methylpropyl, and 2-hydroxy-2-methylpropyl. Alternatively, for certain of these embodiments, R_1 is selected from the group consisting of (1-hydroxycyclobutyl)methyl, (1-hydroxycyclopentyl)methyl, and (1-hydroxycyclohexyl)methyl.

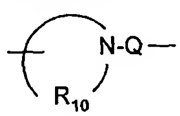
For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, aryl, heteroaryl, hydroxy, and oxo, except where R_1 as defined does not include this definition. For certain of these embodiments as well as any one of the above embodiments wherein R_1 as defined includes heterocyclyl, heterocyclyl is selected

from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and morpholinyl, each of which is unsubstituted or substituted by one, two, or three substituents selected from the group consisting of alkyl, aryl, heteroaryl, and oxo. For certain of these embodiments wherein R_1 is heterocyclylalkylenyl, heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and morpholinyl, and alkylenyl is C_{1-4} alkylenyl. For certain of these embodiments, R_1 is selected from the group consisting of tetrahydro-2*H*-pyran-4-ylmethyl and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl. Alternatively, for certain of these embodiments, R_1 is (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl.

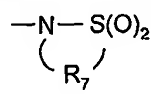
For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is -X-Y-R_4, except where R_1 as defined does not include this definition, wherein X is C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl. For certain of these embodiments, R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, and 2,2-dimethyl-3-(methylsulfonyl)propy.

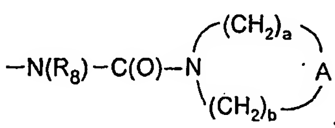
For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is -X-Y-R_4, except where R_1 as defined does not include this definition, wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-,

-N(R_8)-S(O)$_2$-N(R_8)-, -S(O)$_2$-, and  wherein Q is -C(O)-, -C(O)-NH-, or S(O)$_2$-, R_{10} is pentylene, R_8 is hydrogen or methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl. For certain of these embodiments, X is C_{1-6} alkylene, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)-, and R_4 is selected from the group consisting of C_{1-4} alkyl, hydroxyC_{1-4} alkyl, pyridinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl. Alternatively, for certain of these embodiments, X is C_{1-6} alkylene, Y is  wherein Q is -C(O)-, -C(O)-NH-, or S(O)$_2$-, and R_{10} is pentylene, and R_4 is C_{1-4} alkyl. For certain of these embodiments where Y is

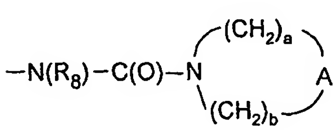


, X is methylene. Alternatively, for certain of these embodiments, Y is -NH-S(O)$_2$-N(R_8)-, R_8 is methyl, and R_4 is C_{1-4} alkyl. For certain of these embodiments where Y is -NH-S(O)$_2$-N(R_8)-, X is C_{2-6} alkylene.

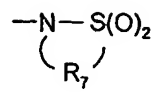
For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is -X-R_5, except where R_1 as defined does not include this definition, wherein X is C_{1-6} alkylene, and R_5 is  or

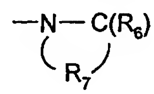


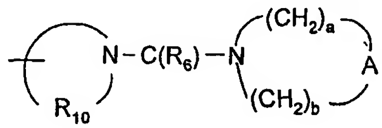
. For certain of these embodiments, R_5 is



wherein R_8 is hydrogen, A is -O-, -CH$_2$-, or -N(Q-R_4)-, and a and b are each 2. For certain of these embodiments, Q-R_4 is methyl. Alternatively, for

certain of these embodiments, R_5 is . For certain of these embodiments, R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

For certain embodiments of any one of the above methods, including any one of the above embodiments, R_1 is -X-R_5, except where R_1 as defined does not include this definition, wherein X is C_{1-4} alkylene, and R_5 is  or

 wherein R_6 is =O, R_7 is propylene, R_{10} is pentylene, A is -O-, and a and b are each 2. For certain of these embodiments, X is ethylene or butylene.

For certain embodiments of any one of the above methods, including any one of the above embodiments having an R_3 group, R_3 is selected from the group consisting of aryl, arylalkyleneoxy, heteroaryl, and heteroaryalkyleneoxy, wherein aryl, arylalkyleneoxy, heteroaryl, and heteroarylalkylenoxy are unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl. For certain of these embodiments, R_3 is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, quinolin-3-yl, or thiazol-4-ylmethoxy, any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl. For certain of these embodiments, R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, quinolin-3-yl, and thiazol-4-ylmethoxy.

For certain embodiments of any one of the above methods, including any one of the above embodiments having an R_3 group, R_3 is thien-3-yl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, hydroxy, and hydroxyalkyl, except where R_3 as defined does not include this definition.

For certain embodiments of any one of the above methods, including any one of the above embodiments having an R_3 group, R_3 is -Z-X-Y-R_4, except where R_3 as defined

does not include this definition, wherein Z is a bond, X is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, morpholin-4-yl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl. For certain of these embodiments, R_3 is 2-(4-morpholinecarbonyl)phenyl.

For certain embodiments of any one of the above methods, including any one of the above embodiments having an R_3 group, except where R_3 as defined does not include this definition, R_3 is -X-Y-R_4, wherein X is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl; with the proviso that when Y is -C(O)-N(R_8)- or -N(R_8)-C(O)-N(R_8)- then R_4 can also be hydrogen; and with the further proviso that when Y is -C(O)- or -N(R_8)-C(O)- then R_4 can also be morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl. For certain of these embodiments, Y is -C(O)-NH-, and R_4 is hydrogen or C_{1-4} alkyl. For certain of these embodiments, R_4 is hydrogen. Alternatively, for certain of these embodiments, Y is -NH-C(O)-, and R_4 is C_{1-4} alkyl. Alternatively, for certain of these embodiments, Y is -C(O)-, and R_4 is morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl. For certain of these embodiments, R_3 is 3-(methylsulfonylamino)phenyl, 3-(pyrrolidin-1-ylcarbonyl)phenyl, or 3-(morpholin-4-ylcarbonyl)phenyl.

For certain embodiments of any one of the above methods, including any one of the above embodiments which includes an R group, R is not present.

For certain embodiments of any one of the above methods, including any one of the above embodiments which includes an R group and an R_3 group, neither R_3 nor R is present.

For certain embodiments of any one of the above methods, including any one of the above embodiments which includes an R group, R is selected from the group consisting of hydroxy and methoxy.

For certain embodiments of any one of the above methods, including any one of the above embodiments which includes an R_3 group, R_3 is not present.

For certain embodiments of any one of the above methods, including any one of the above embodiments, an effective amount of the compound or salt is administered as a pharmaceutical composition comprising a therapeutically effective amount of the compound or salt and a pharmaceutically acceptable carrier.

For certain embodiments, the present invention provides a method of treating a viral disease in an animal in need thereof comprising preferentially inducing the biosynthesis of IFN-α in the animal according to any one of the above methods.

For certain embodiments, the present invention provides a method of treating a neoplastic disease in an animal in need thereof comprising preferentially inducing the biosynthesis of IFN-α in the animal according to any one of the above methods.

For certain embodiments of any one of the above methods, including any one of the above embodiments, the compound or salt is administered systemically.

For certain embodiments, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments, R_A and R_B form a fused aryl ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments R_A and R_B form a fused benzene ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments R_A and R_B form a fused benzene ring which is unsubstituted.

For certain embodiments R_A and R_B form a fused benzene ring which is substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments R_A and R_B form a fused benzene ring which is substituted by one R_3 group. For certain of these embodiments, the R_3 group is at the 7-position.

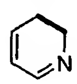
For certain embodiments R_A and R_B form a fused benzene ring which is substituted by one or more R groups.

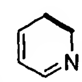
For certain embodiments, R_A and R_B form a fused heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments, R_A and R_B form a fused pyridine ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments, R_A and R_B form a fused pyridine ring which is unsubstituted.

For certain embodiments, R_A and R_B form a fused pyridine ring which is substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group. For certain of these embodiments, the fused pyridine ring is



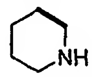
, wherein the highlighted bond is the position where the ring is fused. For certain or these embodiments, R_A and R_B form a fused pyridine ring which is substituted by one R_3 group. For certain of these embodiments, the fused pyridine ring is  , wherein the highlighted bond is the position where the ring is fused. For certain of these embodiments, the R_3 group is at the 7-position.

For certain embodiments, R_A and R_B form a fused pyridine ring which is substituted by one or more R groups.

For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted at a carbon atom by one or more R groups.

For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, wherein the ring is unsubstituted or substituted by one or more R groups. For certain of these embodiments, the fused ring is a cyclohexene ring wherein the double bond is the position where the ring is fused. For certain of these embodiments, the fused cyclohexene ring is unsubstituted.

For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, containing one nitrogen atom, and unsubstituted or substituted at a carbon atom by one or more R groups. For certain of these embodiments, the fused ring is a

tetrahydropyridine ring. For certain of these embodiments, the fused tetrahydropyridine ring is 

, wherein the highlighted bond indicates the position where the ring is fused. For certain of these embodiments, the fused tetrahydropyridine ring is unsubstituted.

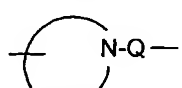
For certain embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain of these embodiments, R_A and R_B are each independently alkyl. For certain of these embodiments, R_A and R_B are each methyl.

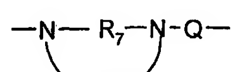
For certain embodiments, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R is selected from the group consisting of hydroxy and methoxy.

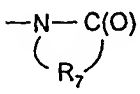
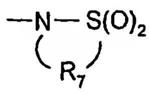
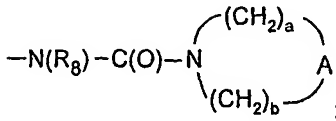
For certain embodiments, R is not present.

For certain embodiments, R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X-Y-R_4$, and $-X-R_5$.

For certain embodiments, R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X^1-Y^1-R_4$, and $-X-R_5$; wherein X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group; Y is selected from the group consisting of -O-, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, -C(O)-, -C(O)-O-, -O-C(O)-, $-N(R_8)-Q-$, $-C(O)-N(R_8)-$, 

, and 

; X^1 is selected from the group consisting of alkylene and arylene; Y^1 is selected from the group consisting of -S-, -C(O)-, -C(O)-O-, $-C(O)-N(R_8)-$, $-S(O)_2-N(R_8)-$, and $-N(R_8)-C(O)-$; R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo; R_5 is selected from the group consisting of:

 ,  , and  ; R_6 is selected from the group consisting of =O and =S; R_7 is C_{2-7} alkylene; R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl; R_{10} is C_{3-8} alkylene; A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-; Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-; W is selected from the group consisting of a bond and -C(O)-; and a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7.

For certain embodiments, R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, dihydroxyC_{1-4}alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one, two, or three substituents selected from the group consisting of alkyl, aryl, heteroaryl, and oxo.

For certain embodiments, R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 2-fluoro-2-methylpropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-(methylsulfonyl)ethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 2,2-dimethyl-3-(methylsulfonyl)propyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 2-

[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-{[(1-methylethyl)sulfonyl]amino}ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-methyl-2-[(ethylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-({[(1-methylethyl)amino]carbonyl}amino)ethyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, tetrahydro-2*H*-pyran-4-ylmethyl, 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

For certain embodiments, R_1 is -R_4.

For certain embodiments, R_1 is selected from the group consisting of alkyl, aminoalkyl, dihydroxyalkyl, haloalkyl, and hydroxyalkyl.

For certain embodiments, R_1 is selected from the group consisting of methyl, ethyl, n-propyl, n-butyl, 2-methylpropyl, 2-amino-2-methylpropyl, 3-amino-2,2-dimethylpropyl, 2,3-dihydroxypropyl, 2-fluoro-2-methylpropyl, and 2-hydroxy-2-methylpropyl.

For certain embodiments, R_1 is selected from the group consisting of (1-hydroxycyclobutyl)methyl, (1-hydroxycyclopentyl)methyl, and (1-hydroxycyclohexyl)methyl.

For certain embodiments, R_1 is heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, aryl, heteroaryl, hydroxy, and oxo.

For certain embodiments, R_1 is heterocyclylalkylenyl wherein heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and morpholinyl, and alkylenyl is C_{1-4} alkylenyl.

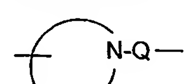
For certain embodiments, R_1 is selected from the group consisting of tetrahydro-2*H*-pyran-4-ylmethyl and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl.

For certain embodiments, R_1 is (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl.

For certain embodiments, R_1 is -X-Y-R_4.

For certain embodiments, R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

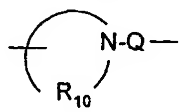
For certain embodiments, R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

For certain embodiments, R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, -S(O)$_2$-, and 

wherein Q is -C(O)-, -C(O)-NH-, or S(O)$_2$-, R_{10} is pentylene, R_8 is hydrogen or methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl

substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

For certain embodiments, R_1 is -X-Y-R_4 wherein X is C_{1-4} alkylene; Y is

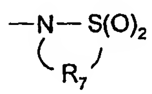


; and R_4 is C_{1-4} alkyl. For certain of these embodiments, R_{10} is pentylene, and Q is selected from the group consisting of -S(O)$_2$-, -C(O)-, and -C(O)-NH-.

For certain embodiments, R_1 is -X-Y-R_4 wherein Y is -NH-S(O)$_2$-N(R_8)-, R_8 is methyl, and R_4 is C_{1-4} alkyl.

For certain embodiments, R_1 is -X-R_5.

For certain embodiments, R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is



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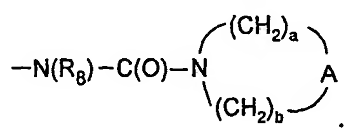

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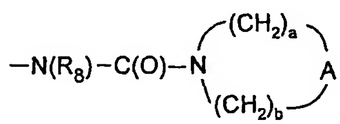
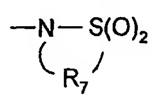
For certain embodiments, R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is



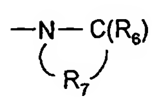
wherein R_8 is hydrogen, A is -O-, -CH$_2$-, or -N(Q-R_4)-, and a and b are each 2.

For certain embodiments, R_1 is -X-R_5 wherein X is C_{1-6} alkylene, R_5 is



, and R_7 is propylene.

For certain embodiments, R_1 is -X-R_5, wherein X is C_{1-4} alkylene, and R_5 is



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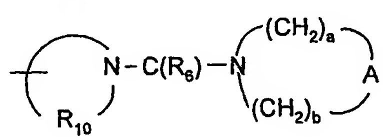


wherein R_6 is =O, R_7 is propylene, R_{10} is pentylene, A is -O-, and a and b are each 2.

For certain embodiments, R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

For certain embodiments, R_3 is selected from the group consisting of -Z-R_4, -Z-X-R_4, -Z-X-Y-R_4, -Z-X-Y-X-Y-R_4, and -Z-X-R_5.

For certain embodiments, R_3 is -Z-R_4.

For certain embodiments, R_3 is selected from the group consisting of aryl, arylalkyleneoxy, heteroaryl, and heteroarylalkyleneoxy, wherein aryl, arylalkyleneoxy, heteroaryl, and heteroarylalkyleneoxy are unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is selected from the group consisting of aryl, arylalkyleneoxy, and heteroaryl, wherein aryl, arylalkyleneoxy, and heteroaryl are unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is thien-3-yl, phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, quinolin-3-yl, or thiazol-4-ylmethoxy, any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, quinolin-3-yl, or thiazol-4-ylmethoxy.

For certain embodiments, R_3 is -Z-X-Y-R_4.

For certain embodiments, R_3 is -Z-X-Y-R_4 wherein X is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; Z is a bond; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, morpholin-4-yl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is -Z-X-Y-R_4 wherein X is phenylene, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; Z is a bond; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_3 is -Z-X-Y-R_4, wherein Z is a bond, X is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl; with the proviso that when Y is -C(O)-N(R_8)- or -N(R_8)-C(O)-N(R_8)- then R_4 can also be hydrogen; and with the further proviso that when Y is -C(O)- or -N(R_8)-C(O)- then R_4 can also be morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

For certain embodiments, R_3 is -Z-X-Y-R_4, wherein Z is a bond, X is phenylene, Y is -C(O)-NH-, and R_4 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_3 is -Z-X-Y-R_4, wherein Z is a bond, X is phenylene, Y is -NH-C(O)-, and R_4 is C_{1-4} alkyl.

For certain embodiments, R_3 is -Z-X-Y-R_4, wherein Z is a bond, X is phenylene, Y is -C(O)-, and R_4 is morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

For certain embodiments, R_3 is 3-(methylsulfonylamino)phenyl, 3-(pyrrolidin-1-ylcarbonyl)phenyl, or 3-(morpholin-4-ylcarbonyl)phenyl.

For certain embodiments, R_3 is 2-(4-morpholinecarbonyl)phenyl.

For certain embodiments, R_3 is not present.

For certain embodiments, neither R_3 nor R is present.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl,

wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl, alkenyl, and heterocyclyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, wherein the alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, and heteroarylalkylenyl, groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, amino, alkylamino, dialkylamino, and, in the case of alkyl and alkenyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, morpholin-4-yl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

For certain embodiments, R_4 is morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

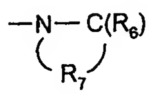
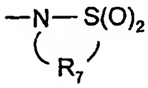
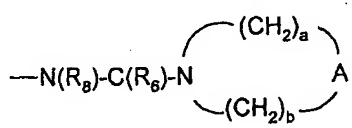
For certain embodiments, R_4 is C_{1-6} alkyl.

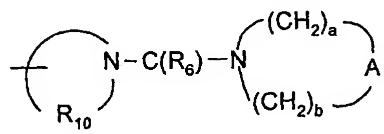
For certain embodiments, R_4 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_4 is C_{1-4} alkyl.

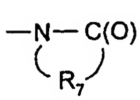
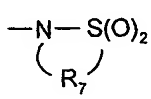
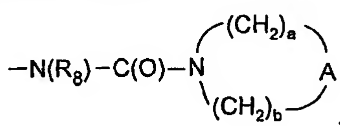
For certain embodiments, R_4 is hydrogen.

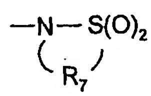
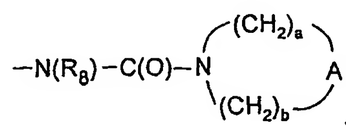
For certain embodiments, R_5 is selected from the group consisting of:

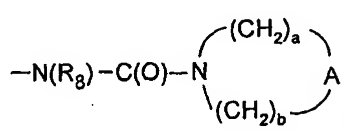
, , , and

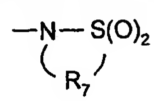
.

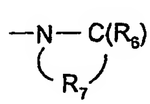
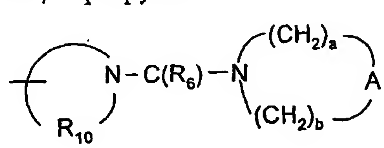
For certain embodiments, R_5 is selected from the group consisting of:

, , and .

For certain embodiments, R_5 is  or .

For certain embodiments, R_5 is  wherein R_8 is hydrogen, A is -O-, $-CH_2-$, or $-N(Q-R_4)-$, and a and b are each 2.

For certain embodiments, R_5 is , and R_7 is propylene.

For certain embodiments, R_5 is  or  wherein R_6 is =O, R_7 is propylene, R_{10} is pentylene, A is -O-, and a and b are each 2.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_6 is =O.

For certain embodiments, R_6 is =S.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_7 is C_{2-4} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

For certain embodiments, R_8 is hydrogen or C_{1-4} alkyl.

For certain embodiments, R_8 is selected from hydrogen and methyl

For certain embodiments, R_8 is methyl.

For certain embodiments, R_8 is hydrogen.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{10} is C_{4-6} alkylene.

For certain embodiments; R_{10} is pentylene.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$.

For certain embodiments, A is -O-, $-CH_2-$, -S-, or $-S(O)_2-$.

For certain embodiments, A is -O-, $-CH_2-$, or $-N(Q-R_4)-$.

For certain embodiments, A is -O- or $-S(O)_2-$.

For certain embodiments, A is -O-.

For certain embodiments, A is $-CH_2-$.

For certain embodiments, A is $-N(Q-R_4)-$.

For certain embodiments, A is $-N(CH_3)-$.

For certain embodiments, A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$.

For certain embodiments, including any one of the above embodiments of Formula II, G_1 is selected from the group consisting of -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY',

-CH(OC$_{1-4}$ alkyl)Y$_0$, -CH$_2$Y$_1$, and -CH(CH$_3$)Y$_1$; R' and R" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and –S(O)$_2$-NH$_2$, with the proviso that R" can also be hydrogen; α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y' is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl; Y$_0$ is selected from the group consisting of C$_{1-6}$ alkyl, carboxy-C$_{1-6}$ alkylenyl, amino-C$_{1-4}$ alkylenyl, mono-*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl, and di-*N,N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl; and Y$_1$ is selected from the group consisting of mono-*N*-C$_{1-6}$ alkylamino, di-*N,N*-C$_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C$_{1-4}$ alkylpiperazin-1-yl.

For certain embodiments, including any one of the above embodiments of Formula II, G$_1$ is selected from the group consisting of -C(O)-R', α-aminoacyl, and -C(O)-O-R'. For certain of these embodiments, R' contains one to ten carbon atoms. For certain of these embodiments, α-aminoacyl is an α-C$_{2-11}$ aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids containing a total of at least 2 carbon atoms and a total of up to 11 carbon atoms, and may also include one or more heteroatoms selected from the group consisting of O, S, and N.

For certain embodiments, including any one of the above embodiments of Formula III, G$_2$ is selected from the group consisting of -X$_2$-C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -X$_2$-C(O)-O-R', and -C(O)-N(R")R'. For certain of these embodiments, X$_2$ is selected from the group consisting of a bond; -CH$_2$-O-; -CH(CH$_3$)-O-; -C(CH$_3$)$_2$-O-; and, in the case of -X$_2$-C(O)-O-R', -CH$_2$-NH-; R' and R" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$,

$-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R" can also be hydrogen; and α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of -C(O)-R' and α-aminoacyl, wherein R' is C_{1-6} alkyl or phenyl which is unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$.

For certain embodiments, including any one of the above embodiments of Formula III, G_2 is selected from the group consisting of α-amino-C_{2-5} alkanoyl, C_{2-6} alkanoyl, C_{1-6} alkoxycarbonyl, and C_{1-6} alkylcarbamoyl.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from a naturally occuring α-amino acid selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, including any one of the above embodiments which include an α-aminoacyl group, α-aminoacyl is an α-aminoacyl group derived from an α-amino acid found in proteins, wherein the the amino acid is selected from the group consisting of racemic, D-, and L-amino acids.

For certain embodiments, the hydrogen atom of the hydroxy group of Formula II (including any one of its embodiments) is replaced by G_2, wherein G_2 is defined as in any one of the above embodiments of G_2.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2$, $-C(R_6)-N(R_8)-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-S-$.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, and $-C(R_6)-N(R_8)-$.

For certain embodiments, Q is selected from the group consisting of -C(O)-,

$-S(O)_2-$, and $-C(O)-N(R_8)-$. In certain of these embodiments, R_8 is hydrogen or methyl.

For certain embodiments, Q is selected from the group consisting of $-S(O)_2-$, $-C(O)-$, and $-C(O)-NH-$.

For certain embodiments, Q is $-C(O)-$.

For certain embodiments, Q is $-S(O)_2-$.

For certain embodiments, Q is $-C(R_6)-N(R_8)-$.

For certain embodiments, Q is $-C(O)-N(R_8)-$ wherein R_8 is hydrogen or methyl.

For certain embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$.

For certain embodiments, V is $-C(R_6)-$.

For certain embodiments, W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$.

For certain embodiments, W is a bond.

For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups.

For certain embodiments, X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group.

For certain embodiments, X is C_{1-6} alkylene which may be interrupted by one -O- group.

For certain embodiments, X is C_{1-6} alkylene.

For certain embodiments, X is C_{2-6} alkylene.

For certain embodiments, X is C_{1-4} alkylene.

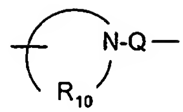
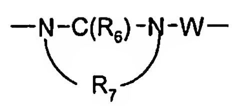
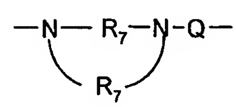
For certain embodiments, X is phenylene.

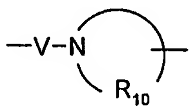
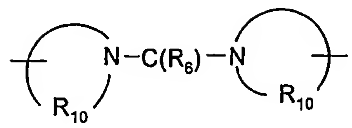
For certain embodiments, X is methylene.

For certain embodiments, X is ethylene.

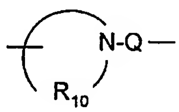
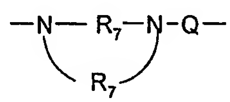
For certain embodiments, X is butylene.

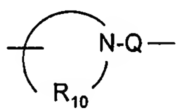
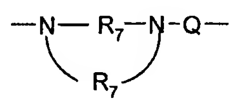
For certain embodiments, Y is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$,

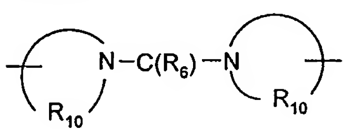
-CH(-N(-O-R_8)-Q-R_4)-, , , ,

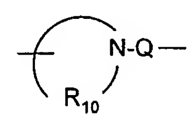
, and .

For certain embodiments, Y is selected from the group consisting of -O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, -C(O)-, -C(O)-O-, -O-C(O)-, -N(R_8)-Q-, -C(O)-N(R_8)-,

, and .

For certain embodiments, Y is selected from the group consisting of -O-,-C(R_6)-, -S(O)$_{0-2}$-, -N(R_8)-Q-, , , and

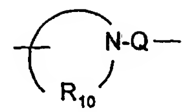
.

For certain embodiments, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, -S(O)$_2$-, and . In certain of these embodiments, Q is -C(O)-, -C(O)-NH-, or S(O)$_2$-, R_{10} is pentylene, and R_8 is hydrogen or methyl.

For certain embodiments, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$-. In certain of these embodiments, R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-,-N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)-. In certain of these embodiments, R_8 is selected from hydrogen and methyl.

For certain embodiments, Y is  . For certain of these embodiments, R_{10} is pentylene, and Q is selected from the group consisting of -S(O)$_2$-, -C(O)-, and -C(O)-NH-.

For certain embodiments, Y is -NH-S(O)$_2$-N(R_8)-. In certain of these embodiments, R_8 is methyl.

For certain embodiments, Y^1 is selected from the group consisting of -S-, -C(O)-, -C(O)-O-, -C(O)-N(R_8)-, -S(O)$_2$-N(R_8)-, and -N(R_8)-C(O)-.

For certain embodiments, Z is a bond or -O-.

For certain embodiments, Z is a bond.

Fro certain embodiments, Z is -O-.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, a and b are each independently 1 to 3.

For certain embodiments, a and b are each 2.

For certain embodiments, a is 1, 2, or 3, and b is 2.

For certain embodiments, n is 1 or 2.

For certain embodiments, n is 1.

For certain embodiments, n is 2.

For certain embodiments, the compound, 1-[4-amino-2-hydroxymethyl-7-(thiazol-4-ylmethoxy)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol, pharmaceutically acceptable salts thereof, pharmaceutical compositions containing this compound or salt thereof in combination with a pharmaceutically acceptable carrier, and the use of this compound in the methods described herein are provided.

Preparation of the Compounds

Compounds of the invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wisconsin, USA) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by

methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, New York, (1967-1999 ed.); Alan R. Katritsky, Otto Meth-Cohn, Charles W. Rees, *Comprehensive Organic Functional Group Transformations*, v. 1-6, Pergamon Press, Oxford, England, (1995); Barry M. Trost and Ian Fleming, *Comprehensive Organic Synthesis*, v. 1-8, Pergamon Press, Oxford, England, (1991); or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. Ed. Springer-Verlag, Berlin, Germany, including supplements (also available via the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For more detailed description of the individual reaction steps, see the EXAMPLES section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds of the invention. Although specific starting materials and reagents are depicted in the reaction schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional methods well known to those skilled in the art.

In the preparation of compounds of the invention it may sometimes be necessary to protect a particular functionality while reacting other functional groups on an intermediate. The need for such protection will vary depending on the nature of the particular functional group and the conditions of the reaction step. Suitable amino protecting groups include acetyl, trifluoroacetyl, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl, and 9-fluorenylmethoxycarbonyl (Fmoc). Suitable hydroxy protecting groups include acetyl and silyl groups such as the *tert*-butyl dimethylsilyl group. For a general description of protecting groups and their use, see T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, USA, 1991.

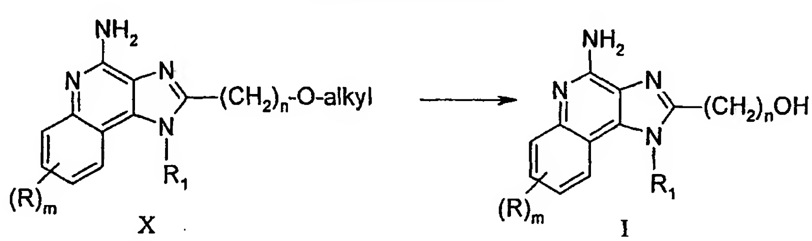
Conventional methods and techniques of separation and purification can be used to isolate compounds of the invention, as well as various intermediates related thereto. Such techniques may include, for example, all types of chromatography (high performance liquid chromatography (HPLC), column chromatography using common absorbents such as silica gel, and thin layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

In some embodiments, compounds of the invention can be prepared according to Reaction Scheme I, wherein R_1, R, m, and n are as defined above and alkyl is methyl or ethyl.

In Reaction Scheme I an ether substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X is cleaved to provide a hydroxyalkyl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I. The reaction is conveniently carried out by adding a solution of boron tribromide in a suitable solvent such as dichloromethane to a solution or suspension of a compound of Formula X in a suitable solvent such as dichloromethane at ambient or at a sub-ambient temperature, for example, at 0°C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Numerous compounds of Formula X are known; others can be prepared using known synthetic methods. See, for example, United States Patent Nos. 6,069,149; 6,331,539; 6,451,810; 6,541,485; 6,756,382; 6,677,349; 6,573,273; 6,664,264; 6,664,265; 6,677,347; 6,660,735; 6,683,088; and 6,667,312 and the references cited therein.

Reaction Scheme I

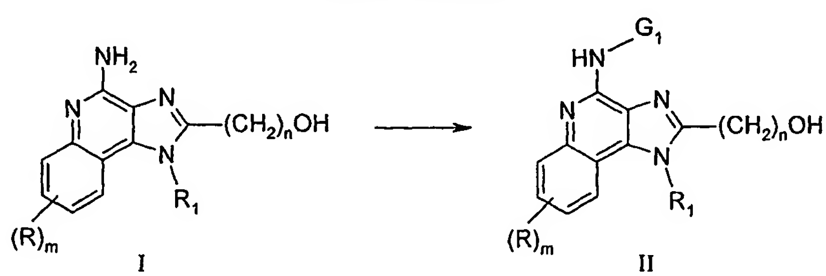


In some embodiments, compounds of the invention can be prepared according to Reaction Scheme II, wherein R_1, G_1, and n are as defined above. Compounds of Formula I can be prepared according to the method described above. The amino group of a compound of Formula I can be converted by conventional methods to a functional group such as an amide, carbamate, urea, amidine, or another hydrolyzable group. A compound of this type can be made by the replacement of a hydrogen atom in an amino group with a group such as -C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -C(O)-O-R', -C(O)-N(R")R', -C(=NY')-R', -CH(OH)-C(O)-OY', -CH(OC$_{1-4}$ alkyl)Y_0, -CH$_2$$Y_1$, and -CH(CH$_3$)$Y_1$; wherein R' and R" are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the

group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –$S(O)_2$-NH_2, with the proviso that R" can also be hydrogen; each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids; Y' is selected from the group consisting of hydrogen, C_{1-6} alkyl, and benzyl; Y_0 is selected from the group consisting of C_{1-6} alkyl, carboxy-C_{1-6} alkylenyl, amino-C_{1-4} alkylenyl, mono-*N*-C_{1-6} alkylamino-C_{1-4} alkylenyl, and di-*N,N*-C_{1-6} alkylamino-C_{1-4} alkylenyl; and Y_1 is selected from the group consisting of mono-*N*-C_{1-6} alkylamino, di-*N,N*-C_{1-6} alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C_{1-4} alkylpiperazin-1-yl. Particularly useful compounds of Formula II are amides derived from carboxylic acids containing one to ten carbon atoms, amides derived from amino acids, and carbamates containing one to ten carbon atoms. The reaction can be carried out, for example, by combining a compound of Formula I with a chloroformate or acid chloride, such as ethyl chloroformate or acetyl chloride, in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane at ambient temperature.

Alternatively, the hydroxy group on a compound of Formula I can be protected using a suitable silyl group such as *tert*-butyl dimethylsilyl using conventional methods. The G_1 group may then be installed using conventional methods followed by the removal of the hydroxy protecting group under acidic conditions to provide a compound of Formula II.

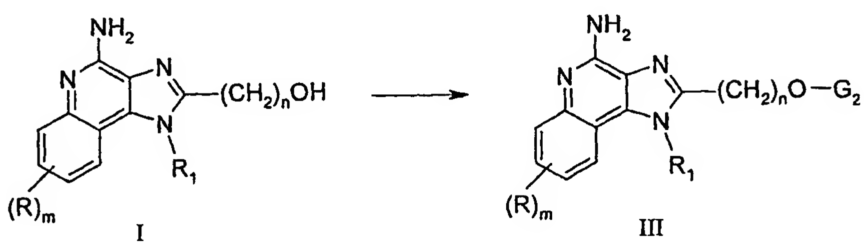
Reaction Scheme II



In some embodiments, compounds of the invention can be prepared according to Reaction Scheme III, wherein R_1, G_2, and n are as defined above. Compounds of Formula I can be prepared according to the method described above. The hydrogen atom of the

alcohol group of a compound of Formula I can be replaced using conventional methods with a group such as X_2-C(O)-R', α-aminoacyl, α-aminoacyl-α-aminoacyl, -X_2-C(O)-O-R', and -C(O)-N(R'')R'; wherein X_2 is selected from the group consisting of a bond; -CH_2-O-; -CH(CH_3)-O-; -C(CH_3)$_2$-O-; and, in the case of -X_2-C(O)-O-R', -CH_2-NH-; R' and R'' are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, -O-C(O)-CH_3, -C(O)-O-CH_3, -C(O)-NH_2, -O-CH_2-C(O)-NH_2, -NH_2, and –S(O)$_2$-NH_2, with the proviso that R'' can also be hydrogen; and each α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids. Particularly useful compounds of Formula III are esters made from carboxylic acids containing one to six carbon atoms, unsubstituted or substituted benzoic acid esters, or esters made from naturally occurring amino acids. For example, the reaction can be carried out by treating a compound of Formula I with a carboxylic acid or amino acid under Mitsunobu reaction conditions by adding triphenylphosphine and a carboxylic acid to a solution or suspension of a compound of Formula I in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate. The reaction can be run at a sub-ambient temperature such as 0 °C.

Reaction Scheme III



In some embodiments, compounds of the invention can also be prepared using the synthetic methods described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt described above in combination with a pharmaceutically acceptable carrier.

The terms “a therapeutically effective amount” and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Cytokine induction can include preferentially inducing the biosynthesis of IFN-α. The exact amount of compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen.

In some embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject.

In other embodiments, the compositions of the invention will contain sufficient active ingredient or prodrug to provide a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, computed according to the Dubois method, in which the body surface area of a subject (m^2) is computed using the subject's body weight: $m^2 = (\text{wt kg}^{0.425} \times \text{height cm}^{0.725}) \times 0.007184$, although in some embodiments the methods may be performed by administering a compound or salt or composition in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/ m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations (e.g., intravenous formulations), syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like. These dosage forms can be prepared with conventional pharmaceutically acceptable carriers and additives using conventional methods, which generally include the step of bringing the active ingredient into association with the carrier.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts described herein may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful for modulating the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders. The compounds or salts of the invention are especially useful as immune response modifiers due to their ability to preferentially induce interferon-α, thus providing a benefit over compounds that also induce pro-inflammatory cytokines (e.g. TNF-α) or that induce pro-inflammatory cytokines at higher levels. While interferon-α and pro-inflammatory cytokines are beneficial in treating certain conditions, interferon-α preferentially induced is believed to be better tolerated by patients, because the significantly lower levels of pro-inflammatory cytokines can result in fewer or less severe adverse side effects experienced by patients. For example, if a subject is treated for a disease (e.g., hepatitis C, metastatic cancer) with a compound that induces significant levels of pro-inflammatory cytokines, while treating the disease, the compound may also cause side effects, such as severe and/or widespread inflammation, tissue destruction, or emesis, that render the subject unable or unwilling to receive the treatment. Alternatively, if a subject is treated with a compound that preferentially induces interferon-α then the compound may treat the disease with less risk of adverse side effects from pro-inflammatory cytokines such as TNF-α. Therefore, by maintaining the ability to treat a condition and reducing adverse side effects, compounds that preferentially induce IFN-α provide an advantage over compounds that would also induce pro-inflammatory cytokines, such as TNF-α, at higher levels.

The ability of the compounds or salts of the invention to preferentially induce the biosynthesis of IFN-α may be particularly advantageous when administered systemically, since adverse side effects, including for example widespread inflammation, may be reduced or even eliminated. Compounds of the invention may be administered

systemically in a number of ways, including but not limited to oral and intravenous administration.

Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, IP-10, MCP-1, and a variety of other cytokines. In some instances, cytokines such as TNF-α, IL-12 may be induced, albeit at significantly reduced levels. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of the invention to the animal. The animal to which the compound or salt is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, the compounds or salts may cause maturation of dendritic cells or proliferation and differentiation of B-lymphocytes.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt or composition and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts or compositions identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus

(e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such as chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a compound or salt identified herein may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic

immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens; toxoids; toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts identified herein may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An animal may also be vaccinated by administering an effective amount of a compound or salt described herein, as a vaccine adjuvant. In one embodiment, there is provided a method of vaccinating an animal comprising administering an effective amount of a compound or salt described herein to the animal as a vaccine adjuvant.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, IP-10, and MCP-1 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments the induction of cytokine biosynthesis may be performed by administering a compound or salt in a dose outside this range. In some of these

embodiments, the method includes administering sufficient compound or salt or composition to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

The invention provides a method of treating a disease which is responsive to the induction of cytokine biosynthesis, particularly the preferential induction of IFN-α, including a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal, comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. In other embodiments, the amount is expected to be a dose of, for example, from about 0.01 mg/m^2 to about 5.0 mg/m^2, (computed according to the Dubois method as described above) although in some embodiments either of these methods may be performed by administering a compound or salt in a dose outside this range. In some of these embodiments, the method includes administering sufficient compound or salt to provide a dose of from about 0.1 mg/m^2 to about 2.0 mg/m^2 to the subject, for example, a dose of from about 0.4 mg/m^2 to about 1.2 mg/m^2.

In addition to the formulations and uses described specifically herein, other formulations, uses, and administration devices suitable for compounds of the present invention are described in, for example, International Publication Nos. WO 03/077944 and WO 02/036592, U.S. Patent No. 6,245,776, and U.S. Publication Nos. 2003/0139364, 2003/185835, 2004/0258698, 2004/0265351, 2004/076633, and 2005/0009858.

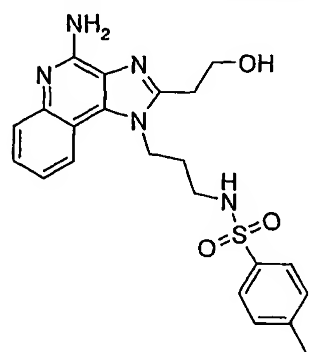
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

In the examples below normal high performance flash chromatography (prep HPLC) was carried out using a COMBIFLASH system (an automated high-performance flash purification product available from Teledyne Isco, Inc., Lincoln, Nebraska, USA) or a HORIZON HPFC system (an automated high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80/18/2 v/v/v chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio.

Example 1

N-{3-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-4-methylbenzenesulfonamide

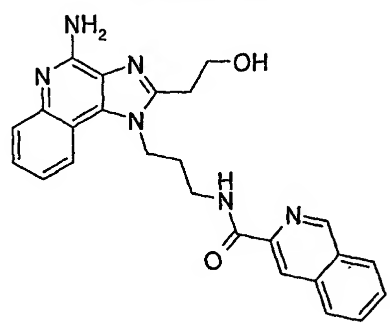


Boron tribromide (5.50 mL of 1 M in dichloromethane) was added dropwise to a chilled (0 °C) suspension of *N*-{3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-4-methylbenzenesulfonamide (1.0 g, 2.2 mmol; U.S. Patent No. 6,677,349, Example 253) in dichloromethane (20 mL). The reaction mixture was stirred at 0 °C for 3 hours. The reaction mixture was quenched with methanol. Hydrochloric acid (about 10 mL of 6 N) was added and the mixture was stirred at 50 °C overnight. The mixture was diluted with water (50 mL) and ethyl acetate (100 mL) and then brought to

neutral pH with solid sodium hydroxide. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a yellow solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 5% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 5 to 10% methanol in dichloromethane containing 1% ammonium hydroxide) to provide a white solid. This material was suspended in hot acetonitrile, allowed to cool, and then the solvent was decanted. The resulting material was dried under vacuum to provide about 200 mg of *N*-{3-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-4-methylbenzenesulfonamide as a white solid, m.p.231-232 °C. Anal. calcd for $C_{22}H_{25}N_5O_3S \cdot 0.20\ CH_4O$: %C, 59.79; %H, 5.85; %N, 15.70. Found: %C, 59.44; %H, 5.89; %N, 15.52.

Example 2

N-{3-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}isoquinoline-3-carboxamide

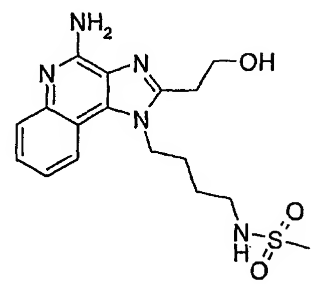


Boron tribromide (5.50 mL of 1 M in dichloromethane) was added dropwise to a chilled (0 °C) suspension of *N*-{3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}isoquinoline-3-carboxamide (1.0 g, 2.2 mmol; U.S. Patent No. 6,756,382, Example 192) in dichloromethane (20 mL). The reaction mixture was stirred at 0 °C for 45 minutes and then allowed to warm to ambient temperature. After 5 hours the reaction mixture was concentrated under reduced pressure and the residue was allowed to stand over the weekend. The residue was diluted with methanol (20 mL) and then heated to 50 °C. Hydrochloric acid (about 10 mL of 6 N) was added and the mixture was stirred for about 2.5 hours. The mixture was made basic with aqueous sodium hydroxide and

then extracted with ethyl acetate (x2). The combined extracts were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a yellow solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 5% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 5 to 10% methanol in dichloromethane containing 1% ammonium hydroxide) to provide a white solid. This material was suspended in hot acetonitrile, allowed to cool, and then the solvent was decanted. The resulting material was dried under vacuum to provide about 400 mg of *N*-{3-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}isoquinoline-3-carboxamide as a white solid, mp 245-246 °C. Anal calcd for $C_{25}H_{24}N_6O_2$: %C, 67.73; %H, 5.59; %N, 18.80; Found: %C, 67.38; %H, 5.54; %N, 18.84.

Example 3

N-{4-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide



Part A

3-Methoxypropionyl chloride (15.4 g, 126 mmol) was added dropwise over a period of 20 minutes to a chilled (ice bath) solution of *tert*-butyl *N*-{4-[(3-aminoquinolin-4-yl)amino]butyl}carbamate (38 g, 115 mmol, U.S. Patent No. 6,541,485, Example 2, Part B) in pyridine. The reaction mixture was stirred for 4 hours and then allowed to stand at ambient temperature over the weekend. Pyridine hydrochloride (3.9 g, 34 mmol) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with dichloromethane (250 mL) and aqueous sodium bicarbonate (250 mL). The layers were separated. The separatory funnel was rinsed with a small amount of methanol to remove a residue coating the walls. The combined organics were concentrated under reduced pressure. The residue was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to

5% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 5 to 10% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 18 g of *tert*-butyl *N*-{4-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate.

Part B

3-Chloroperoxybenzoic acid (20 g of 77%) was added in a single portion to a solution of the material from Part A (18 g, 45.2 mmol) in dichloroethane (170 mL). After 2 hours concentrated ammonium hydroxide (150 mL) was added and the reaction mixture was stirred until the phases were mixed well. *Para*-Toluenesulfonyl chloride (10.6 g, 54 mmol) was added in a single portion along with a small amount of dichloroethane. The reaction mixture was stirred overnight at ambient temperature and then diluted with water and dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane (x2). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 23 g of crude *tert*-butyl *N*-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}carbamate as a red tar.

Part C

The material from Part B was combined with a solution of hydrochloric acid in dioxane (325 mL of 4 M) and stirred at ambient temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30 mL) and 6 M sodium hydroxide was added with stirring to about pH 9. Attempts to extract with dichloromethane and ethyl acetate were not successful. The organic and aqueous layers were concentrated under reduced pressure and combined to provide a dark orange solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 8% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 9 to 35% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 10.65 g of 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an orange solid.

Part D

Triethylamine (10.5 mL, 75.0 mmol) was added to a mixture of a portion (4.7 g, 15 mmol) of the material from Part C in pyridine (50 mL). The reaction mixture was stirred for several minutes and then methanesulfonyl chloride (1.27 mL, 16.5 mmol) was added

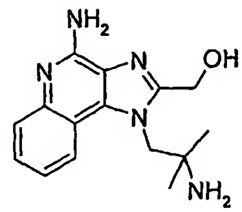
dropwise. The reaction mixture was stirred at ambient temperature for 2 hours and then at 50 °C for 2 hours. More methanesulfonyl chloride (0.5 eq) was added and the reaction mixture was stirred at 50 °C for 2 hours. Another portion of methanesulfonyl chloride (0.25 eq) was added and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with dichloromethane and water. The layers were separated and the aqueous layer was extracted with dichloromethane (x3). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 5 g of crude *N*-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide as a red oil.

Part E

Boron tribromide (22.4 mL of 1 M in dichloromethane) was added slowly to a chilled (ice bath) mixture of a portion of the material from Part D (3.5 g, about 8.9 mmol) and dichloromethane (50 mL). After the addition was complete the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol and then combined with hydrochloric acid (50 mL of 6 M). The mixture was stirred at 50 °C for 2 hours and then concentrated under reduced pressure. The residue was combined with ammonia in methanol (about 50 mL of 7 M) to neutralize the acid and then concentrated. This procedure was repeated 3 times. The crude product was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0 to 10% methanol in dichloromethane containing 1% ammonium hydroxide). The product was stirred with hot acetonitrile, allowed to stand overnight, and then isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to provide 1.1 g of *N*-{4-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide, mp 206-208 °C. Anal calcd for $C_{17}H_{23}N_5O_3S$: %C, 54.09; %H, 6.14; %N, 18.55. Found: %C, 53.83; %H, 6.29; %N, 18.29.

Example 4

1-(2-Amino-2-methylpropyl)-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Under a nitrogen atmosphere, triethylamine (6.6 mL, 47 mmol) was added slowly to a solution of 2,4-dichloro-3-nitroquinoline (10.0 g, 41.1 mmol) in anhydrous 1-methyl-2-pyrrolidinone (40 mL). The reaction mixture was cooled to 0 °C with an ice bath. A solution of 1,2-diamino-2-methylpropane (4.1 g, 47.3 mmol) in anhydrous 1-methyl-2-pyrrolidinone (5 mL) was added dropwise over a period of 15 minutes while maintaining the temperature of the reaction mixture below 4 °C. After the addition was completed the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 4 hours. The reaction mixture was slowly poured into vigorously stirred warm water (300 mL). The resulting suspension was stirred for 1 hour and then cooled to 13 °C by adding ice. The solid was isolated by filtration and then washed with cold water until the filtrate was clear to provide 12.1 g of N^1-(2-chloro-3-nitroquinolin-4-yl)-2-methylpropane-1,2-diamine as a damp yellow solid.

Part B

A solution of sodium hydroxide (1.8 g of solid sodium hydroxide dissolved in 45 mL of water) was added slowly to a solution of the material from Part A (41.1 mmol) in tetrahydrofuran (96 mL). A solution of di-*tert*-butyl dicarbonate (10.8 g, 49.4 mmol) in tetrahydrofuran (30 mL) was added dropwise over a period of 15 minutes. The reaction solution was stirred at ambient temperature. After 6 hours 10% sodium hydroxide (2 mL) and additional di-*tert*-butyl dicarbonate (1.5 g) were added and the reaction solution was stirred at ambient temperature overnight. The layers were separated and the tetrahydrofuran was removed under reduced pressure to provide a mixture. The mixture was diluted with water (200 mL) and then extracted with dichloromethane (2 x 100 mL). The organics were combined, washed sequentially with aqueous sodium carbonate (2 x 150 mL) and brine (100 mL), dried over sodium sulfate and magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was triturated with heptane (75 mL) for 15 minutes at 65 °C and then filtered while hot. The isolated solids were

washed with heptane (20 mL) to provide 13.2 g of *tert*-butyl *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate as a yellow powdery solid.

Part C

A Parr vessel was charged with 5% Pt/C (0.5 g) and acetonitrile (10 mL). A solution of the material from Part B in acetonitrile (450 mL) was added. The vessel was placed on a Parr shaker under hydrogen pressure (40 psi, 2.8 x 10^5 Pa) for 5 hours. The reaction mixture was filtered through a layer of CELITE filter aid to remove the catalyst. The filtrate was carried on to the next step.

Part D

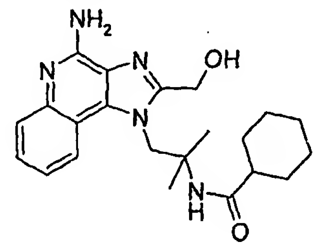
The solution of *tert*-butyl *N*-{2-[(3-amino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate in acetonitrile from Part C was cooled to 5 °C using an ice bath. A solution of acetoxyacetyl chloride (4.8 g, 35.1 mmol) in acetonitrile (20 mL) was added dropwise at a rate such that the temperature of the reaction mixture was maintained at 5 °C. After the addition was complete the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature for 5 hours. The reaction mixture was concentrated under reduced pressure to provide 16.7 g of *N*-{2-[(3-acetoxyacetylamino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate hydrochloride as a yellow powder.

Part E

A mixture of the material from Part D (15.7 g) and ammonia in methanol (235 mL of 7 N) was divided into equal portions and placed in pressure vessels. The vessels were sealed, heated at 160 °C for 20 hrs, and then allowed to cool to ambient temperature overnight. The reaction mixtures were filtered. The isolated solids were washed with water and dried in a vacuum oven at 60 °C overnight to provide 6.0 g of a tan powder. A portion (1 g) was treated with activated charcoal and recrystallized from ethanol (75 mL) to provide 0.5 g of 1-(2-amino-2-methylpropyl)-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white granular solid, mp 248-250 °C. Anal calcd for $C_{15}H_{19}N_5O$: %C, 63.14; %H, 6.71; %N, 24.54. Found: %C, 63.13; %H, 6.81; %N, 24.64.

Example 5

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide

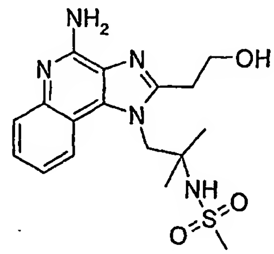


A solution of 1-(2-amino-2-methylpropyl)-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (2.0 g, 7.0 mmol) in 1-methyl-2-pyrrolidinone (30 mL) was cooled to -20 °C. Triethylamine (1.1 mL, 7.7 mmol) was added in a single portion. A chilled (-5 °C) solution of cyclohexanecarbonyl chloride (1.03 g, 7.0 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added dropwise over a period of 20 minutes while maintaining the reaction mixture at -20 °C. The reaction mixture was stirred at ambient temperature overnight. Additional cyclohexanecarbonyl chloride (0.1 g) was added and the reaction mixture stirred for 2 hours. The reaction mixture was poured into water with vigorous stirring. The resulting precipitate was isolated by filtration to provide 1.7 g of an ivory powder. Analysis by high performance liquid chromatography and NMR indicated that the powder was a mixture of the desired product and an ester formed from the reaction of the hydroxy group of the desired product with cyclohexanecarbonyl chloride.

The powder was dissolved in ethanol (25 mL), combined with a solution of sodium hydroxide (0.21 g) in water (25 mL), and then heated at 50 °C for 3 hours. The ethanol was removed under reduced pressure and the solids were isolated by filtration to provide 1.2 g of a light tan powder. The powder was dissolved in a mixture of acetonitrile (100 mL), water (2 mL) and ethanol (25 mL). The solution was allowed to stand overnight and was then concentrated to a volume of 5 mL to provide a white paste. The paste was triturated with warm (70 °C) acetonitrile (50 mL) for 30 minutes, heated to reflux, and then allowed to cool to ambient temperature. The resulting solid was isolated by filtration to provide 1.05 g of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide as a light yellow powder, mp 248-250 °C. Anal calcd for $C_{22}H_{29}N_5O_2$: %C, 66.81; %H, 7.39; %N, 17.71; Found: %C, 66.56; %H, 7.60; %N, 17.82.

Example 6

N-{2-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide



Part A

Triethylamine (39.3 mL, 0.282 mol) was added to a chilled (ice bath) solution of N^1-(2-chloro-3-nitroquinolin-4-yl)-2-methylpropane-1,2-diamine (41.42 g, 0.141 mol) in dichloromethane (about 500 mL). Under a nitrogen atmosphere a solution of methanesulfonic anhydride in (29.47 g, 0.169 mol) in dichloromethane (100 mL) was added via a cannula to the reaction mixture over a period of 45 minutes. After the addition was complete the ice bath was removed and the reaction mixture was allowed to stir at ambient temperature overnight. The reaction mixture was washed sequentially with saturated aqueous sodium bicarbonate (x2) and brine, dried over a mixture of sodium sulfate and magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 46.22 g of an orange solid. This material was recrystallized from toluene (about 1 L), isolated by filtration, rinsed with cold toluene, and dried under high vacuum at 60 °C to provide 33.09 g of *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide.

Part B

A hydrogenation vessel was charged with 5% Pt/C (4.14 g) and a solution of *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (54.59 g, 0.147 mol) in acetonitrile (1800 mL). The vessel was placed under hydrogen pressure (48 psi, 3.3 x 10^5 Pa) overnight. An additional portion (4.25 g) of catalyst was added and the vessel was placed under hydrogen pressure (48 psi, 3.3 x 10^5 Pa) for 4 hours. The reaction mixture was filtered through a layer of CELITE filter aid and the filter cake was rinsed with fresh acetonitrile until the washes were clear.

Part C

Under a nitrogen atmosphere, 3-methoxypropionyl chloride (17.6 mL, 0.162 mol) was added dropwise to the solution of *N*-{2-[(3-amino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (0.147 mol) in acetonitrile (2.2 L) from Part B. The reaction mixture was allowed to stir at ambient temperature over the weekend. The resulting precipitate was isolated by filtration, rinsed with a small amount of acetonitrile, and then dried under high vacuum at 60 °C to provide 55.84 g of *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]quinolin-3-yl}-3-methoxypropionamide.

Part D

A Parr bomb was charged with 25.0 g of *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]aminoquinolin-3-yl}-3-methoxypropionamide and ammonia in methanol (300 mL of 7 N). A second vessel was charged with 30.21 g of *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]quinolin-3-yl}-3-methoxypropionamide and ammonia in methanol (400 mL of 7 N). Both vessels were sealed and then heated at 170 °C for 14 hours. The reaction mixtures were combined and the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 38.16 g of *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as an off white foam.

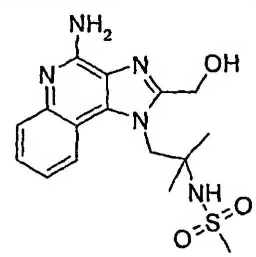
Part E

Under a nitrogen atmosphere, boron tribromide (3.5 mL of 1 M in dichloromethane) was added dropwise to a chilled (0 °C) solution of *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide (0.55 g, 1.40 mmol) in dichloromethane (20 mL). The reaction was allowed to warm to ambient temperature overnight. The reaction was quenched with methanol (10 mL) and the solvent was removed under reduced pressure. The residue was dissolved in hydrochloric acid (6 N), stirred at 50 °C for about 2.5 hours, and then allowed to cool to ambient temperature. The reaction mixture was adjusted to pH 11 with ammonium hydroxide and then extracted with dichloromethane (x 10). The combined organics were washed with brine, dried over sodium sulfate, filtered, and then concentrated under

reduced pressure to provide 0.47 g of a white solid. This material was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 30-50% CMA in chloroform for 15 column volumes followed by 50% CMA in chloroform for 5 column volumes) and then dried under high vacuum to provide 250 mg of *N*-{2-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as white solid, m.p. 209 - 212°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.39 (m, 1H), 7.27 (s, 1H), 7.21 (m, 1H), 6.49 (s, 2H), 4.84 (t, J = 5.4 Hz, 2H), 4.82 (br s, 1H), 3.88 (m, 2H), 3.18 (br s, 2H), 3.00 (s, 3H), 1.27 (br s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.6, 152.0, 145.4, 133.5, 126.9, 126.8, 126.5, 121.3, 120.8, 115.6, 60.5, 57.9, 54.1, 44.8, 31.4, 25.8; MS (ESI) m/z 378 $(M + H)^+$; Anal. calcd for $C_{17}H_{23}N_5O_3S$: %C, 54.09; %H, 6.14; %N, 18.55. Found: %C, 53.76; %H, 6.02; %N, 18.32.

Example 7

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide



Part A

A pressure vessel was charged with a solution of of *N*-{2-[(2-chloro-3-nitroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (5 g, 13 mmol) in acetonitrile (150 mL). Catalyst was added (0.5 g of 5% Pt/C) and the vessel was placed under hydrogen pressure (50 psi, 3.4 X 10^5 Pa) for 2 hours. The reaction mixture was filtered through a layer of CELITE filter aid.

Part B

The solution of *N*-{2-[(3-amino-2-chloroquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide in acetonitrile from Part A was chilled in an ice bath. Acetoxyacetyl chloride (1.5 mL, 14 mmol) was added over a period of 5 minutes. The reaction mixture was allowed to stir for 3 hours. A precipitate was isolated by filtration

and rinsed with acetonitrile to provide crude *N*-{2-chloro-4-[2-(methanesulfonylamino)-2-methylpropyl]quinolin-3-yl}acetoxyacetamide hydrochloride.

Part C

A solution of sodium hydroxide (0.8 g) in water (15 mL) was added to a suspension of the material from Part B in ethanol (60 mL) until all of the solid dissolved. The reaction mixture was heated at 60 °C overnight and then concentrated under reduced pressure. The residue was dissolved in water (50 mL), sodium chloride (10 g) was added, and the mixture was extracted with chloroform (3 x 300 mL). The extracts were concentrated under reduced pressure to provide about 4 g of crude *N*-[2-(4-chloro-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide.

Part D

The material from Part C was combined with a solution of ammonia in methanol (50 mL of 7 N) and heated at 150 °C for 10 hours. The reaction mixture was allowed to cool to ambient temperature. A precipitate was isolated by filtration, rinsed with methanol (20 mL), slurried with water (50 mL), isolated by filtration, washed with water (20 mL), and dried to provide 2.7 g of a brown crystalline solid. This material was combined with methanol (50 mL), heated at 50 °C overnight, and then isolated by filtration to provide 2.3 g of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide, mp 262-265 °C. Anal. calcd for $C_{16}H_{21}N_5O_3S$: %C, 52.88; %H, 5.82; %N, 19.27. Found: %C, 52.64; %H, 5.95; %N, 19.50.

Examples 8 – 72

Part A

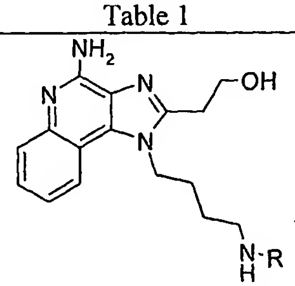
A reagent (1.1 eq) from Table 1 below was added to a test tube containing a solution of 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (73 mg) in *N,N*-dimethylacetamide (1 mL) containing *N,N*-diisopropylethylamine (2 eq). The test tube was placed on a shaker overnight. The solvent was removed by vacuum centrifugation. The reaction mixtures were separated by solid-supported liquid-liquid extraction according to the following procedure. Each sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with de-ionized water (600 µL) for about 20 minutes. After 10 minutes chloroform (500 µL) was added to elute the product from the diatomaceous earth into a well of a collection

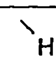
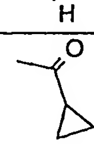
plate. After an additional 10 minutes the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

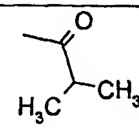
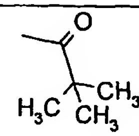
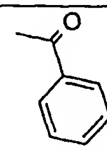
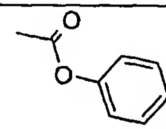
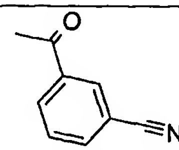
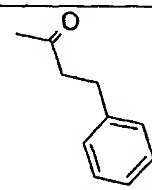
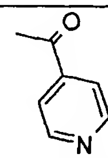
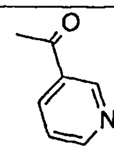
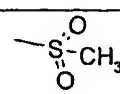
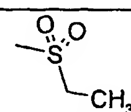
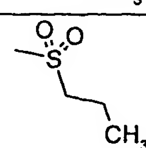
Part B

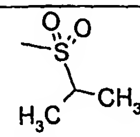
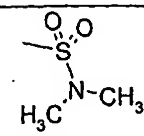
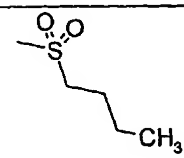
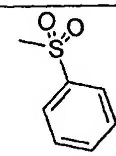
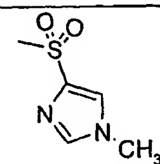
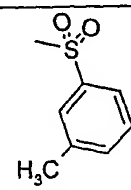
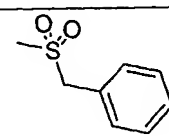
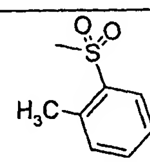
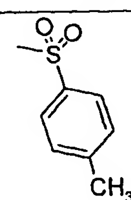
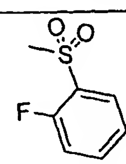
The residue (in a test tube) was combined with dichloromethane (1 mL) and the mixture was sonicated to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 μL of 1 M in heptane). The mixture was shaken for 5 minutes, placed in an ice bath for 30 minutes, and then shaken overnight. The solvents were removed by vacuum centrifugation. The residue was diluted with methanol (1 mL) and hydrochloric acid (500 μL of 6 N). The mixture was shaken for 30 minutes and then the solvents were removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. Table 1 below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

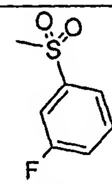
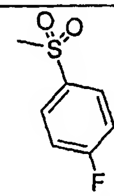
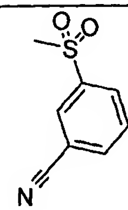
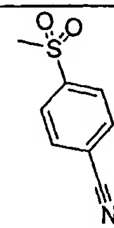
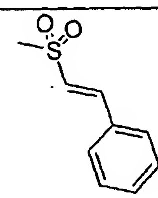
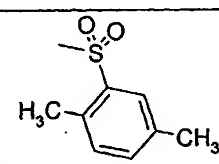
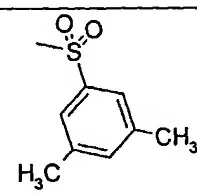
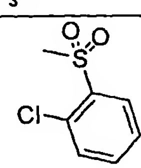
Table 1

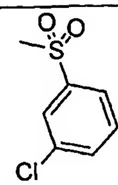
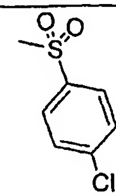
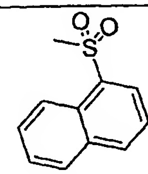
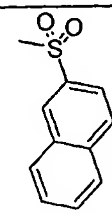
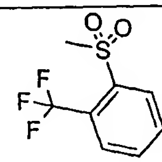
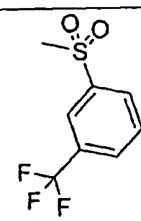
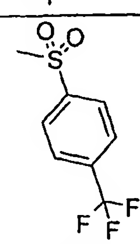
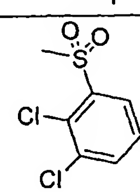


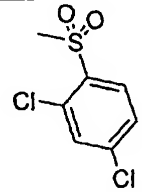
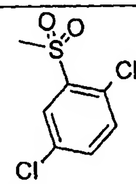
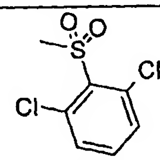
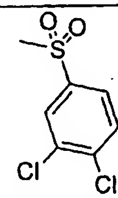
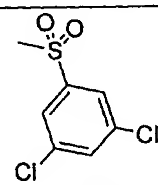
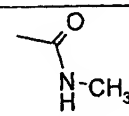
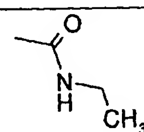
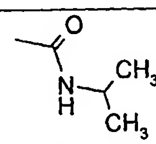
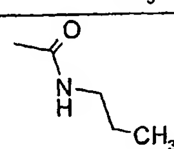
Example	Reagent	R	Measured Mass (M+H)
8	None		300.1840
9	Cyclopropanecarbonyl chloride		368.2063

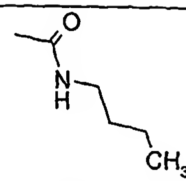
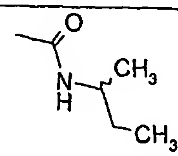
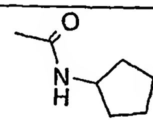
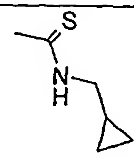
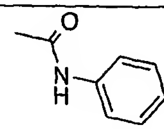
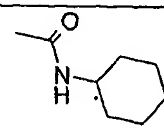
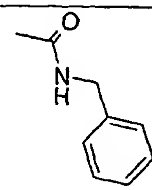
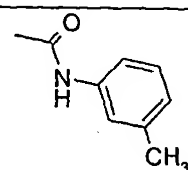
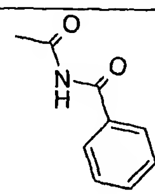
10	Isobutyryl chloride		370.2224
11	Pivaloyl chloride		384.2390
12	Benzoyl chloride		404.2103
13	Phenyl chloroformate		420.2056
14	3-Cyanobenzoyl chloride		429.2031
15	Hydrocinnamoyl chloride		432.2377
16	Isonicotinoyl chloride hydrochloride		405.2071
17	Nicotinoyl chloride hydrochloride		405.2058
18	Methanesulfonyl chloride		378.1592
19	Ethanesulfonyl chloride		392.1729
20	1-Propanesulfonyl chloride		406.1899

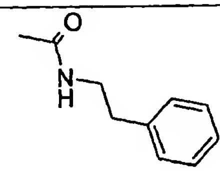
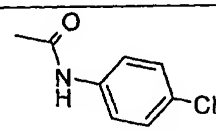
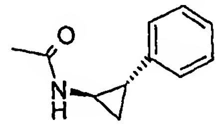
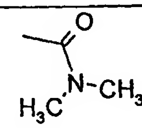
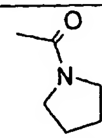
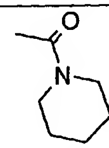
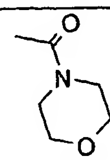
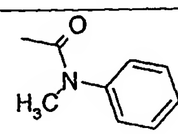
21	Isopropylsulfonyl chloride		406.1888
22	Dimethylsulfamoyl chloride		407.1853
23	1-Butanesulfonyl chloride		420.2050
24	Benzenesulfonyl chloride		440.1741
25	1-Methylimidazole-4-sulfonyl chloride		444.1806
26	3-Methylbenzenesulfonyl chloride		454.1895
27	*alpha*-Toluenesulfonyl chloride		454.1923
28	o-Toluenesulfonyl chloride		454.1944
29	*p*-Toluenesulfonyl chloride		454.1907
30	2-Fluorobenzenesulfonyl chloride		458.1664

31	3-Fluorobenzenesulfonyl chloride		458.1652
32	4-Fluorobenzenesulfonyl chloride		458.1639
33	3-Cyanobenzenesulfonyl chloride		465.1678
34	4-Cyanobenzenesulfonyl chloride		465.1668
35	*beta*-Styrene sulfonyl chloride		466.1895
36	2,5-Dimethylbenzenesulfonyl chloride		468.2063
37	3,5-Dimethylbenzenesulfonyl chloride		468.2046
38	2-Chlorobenzenesulfonyl chloride		474.1351

39	3-Chlorobenzenesulfonyl chloride		474.1385
40	4-Chlorobenzenesulfonyl chloride		474.1390
41	1-Naphthalenesulfonyl chloride		490.1891
42	2-Naphthalenesulfonyl chloride		490.1885
43	2-(Trifluoromethyl)benzenesulfonyl chloride		508.1592
44	3-(Trifluoromethyl)benzenesulfonyl chloride		508.1612
45	4-(Trifluoromethyl)benzenesulfonyl chloride		508.1640
46	2,3-Dichlorobenzenesulfonyl chloride		508.0967

47	2,4-Dichlorobenzenesulfonyl chloride		508.0979
48	2,5-Dichlorobenzenesulfonyl chloride		508.0987
49	2,6-Dichlorobenzenesulfonyl chloride		508.0968
50	3,4-Dichlorobenzenesulfonyl chloride		508.0961
51	3,5-Dichlorobenzenesulfonyl chloride		508.0985
52	Methyl isocyanate		357.2073
53	Ethyl isocyanate		371.2203
54	Isopropyl isocyanate		385.2347
55	*n*-Propyl isocyanate		385.2349

56	*n*-Butyl isocyanate		399.2494
57	*sec*-Butyl isocyanate		399.2517
58	Cyclopentyl isocyanate		411.2516
59	Cyclopropylmethyl isothiocyanate		413.2133
60	Phenyl isocyanate		419.2226
61	Cyclohexyl isocyanate		425.2701
62	Benzyl isocyanate		433.2374
63	*m*-Tolyl isocyanate		433.2344
64	Benzoyl isocyanate		447.2126

65	2-Phenyl ethylisocyanate		447.2512
66	4-Chlorophenyl isocyanate		453.1797
67	*trans*-2-Phenylcyclopropyl isocyanate		459.2518
68	*N,N*-Dimethylcarbamoyl chloride		371.2185
69	1-Pyrrolidinecarbonyl chloride		397.2382
70	1-Piperidinecarbonyl chloride		411.2526
71	4-Morpholinylcarbonyl chloride		413.2330
72	*N*-Methyl-*N*-phenylcarbamoyl chloride		433.2364

Examples 73 – 110

Part A

Tert-Butyl 3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (5 g, U.S. Patent No. 6,573,273, example 148) and hydrochloric acid in dioxane (100 mL of 4 M) were combined and stirred for 4 hours at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (30 mL). The pH was adjusted to pH 8 with 6 M sodium hydroxide. The solution was diluted with dichloromethane, ethyl acetate, triethylamine,

and brine. The organic layer was concentrated under reduced pressure to provide an orange solid. This material was purified by prep HPLC (COMBIFLASH system eluting first with a gradient of 0 to 10% methanol in dichloromethane containing 1% ammonium hydroxide and then with a gradient of 9 to 30% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 1.58 g of 1-(3-aminopropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid.

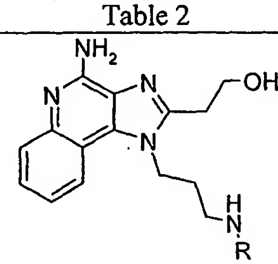
Part B

A reagent (1.1 eq) from Table 2 below was added to a test tube containing a solution of 1-(3-aminopropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (30 mg) in chloroform (1 mL) containing *N,N*-diisopropylethylamine (1.5 eq). The test tube was placed on a shaker overnight. The reaction mixtures were separated by solid-supported liquid-liquid extraction according to the following procedure. Each reaction mixture was loaded onto diatomaceous earth that had been equilibrated with de-ionized water (600 μL) for about 20 minutes. After 10 minutes chloroform (500 μL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

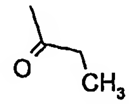
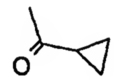
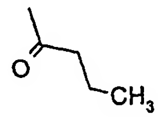
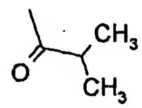
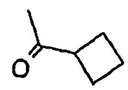
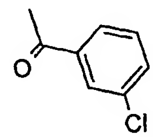
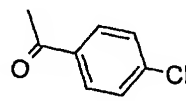
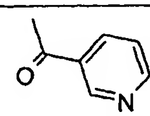
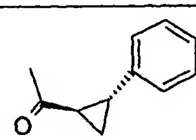
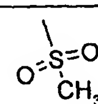
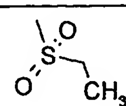
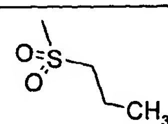
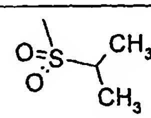
Part C

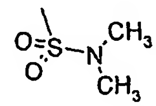
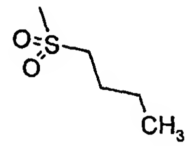
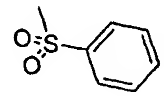
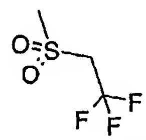
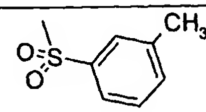
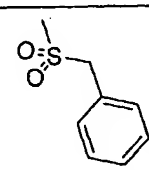
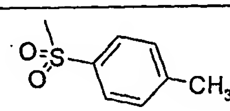
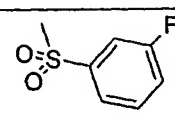
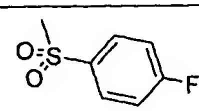
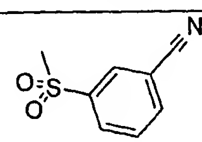
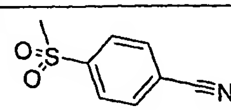
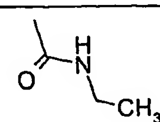
The ether was cleaved and the resulting product was purified using the method of Part B in Examples 8 – 72. Table 2 below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

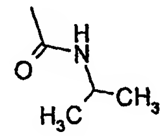
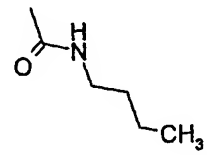
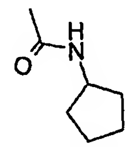
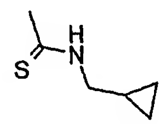
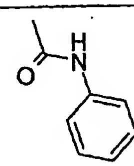
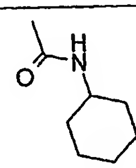
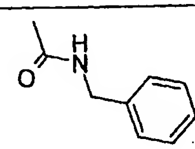
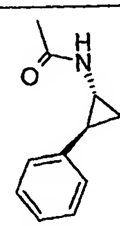
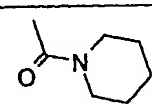
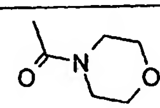
Table 2

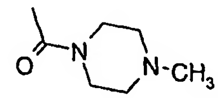
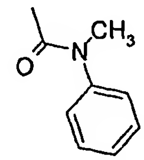


Example	Reagent	R	Measured Mass (M+H)
73	None	H	286.1689

74	Propionyl chloride		342.1956
75	Cyclopropanecarbonyl chloride		354.1946
76	Butyryl chloride		356.2122
77	Isobutyryl chloride		356.2119
78	Cyclobutanecarbonyl chloride		368.2120
79	3-Chlorobenzoyl chloride		424.1570
80	4-Chlorobenzoyl chloride		424.1583
81	Nicotinoyl chloride hydrochloride		391.1913
82	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		430.2257
83	Methanesulfonyl chloride		364.1479
84	Ethanesulfonyl chloride		378.1639
85	1-Propanesulfonyl chloride		392.1783
86	Isopropylsulfonyl chloride		392.1788

87	Dimethylsulfamoyl chloride		393.1715
88	1-Butanesulfonyl chloride		406.1946
89	Benzenesulfonyl chloride		426.1633
90	2,2,2-Trifluoroethanesulfonyl chloride		432.1355
91	3-Methylbenzenesulfonyl chloride		440.1774
92	*alpha*-Toluenesulfonyl chloride		440.1762
93	*p*- Toluenesulfonyl chloride		440.1790
94	3-Fluorobenzenesulfonyl chloride		444.1523
95	4-Fluorobenzenesulfonyl chloride		444.1545
96	3-Cyanobenzenesulfonyl chloride		451.1554
97	4-Cyanobenzenesulfonyl chloride		451.1582
98	Ethyl isocyanate		357.2050

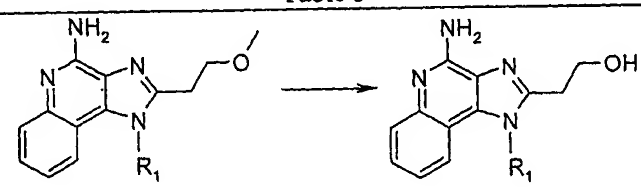
99	Isopropyl isocyanate		371.2234
100	*n*-Butyl isocyanate		385.2364
101	Cyclopentyl isocyanate		397.2359
102	Cyclopropylmethyl isothiocyanate		399.1979
103	Phenyl isocyanate		405.2040
104	Cyclohexyl isocyanate		411.2526
105	Benzyl isocyanate		419.2239
106	*trans*-2-Phenylcyclopropyl isocyanate		445.2388
107	1-Piperidinecarbonyl chloride		397.2384
108	4-Morpholinylcarbonyl chloride		399.2173

109	4-Methyl-1-piperazinecarbonyl chloride		412.2485
110	*N*-Methyl-*N*-phenylcarbamoyl chloride		419.2229

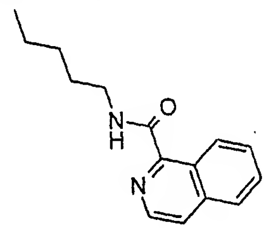
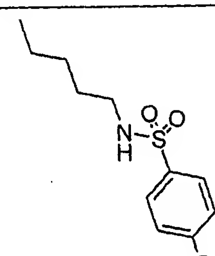
Examples 111 – 140

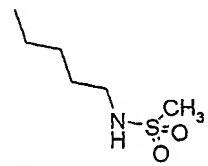
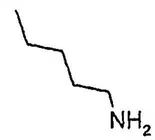
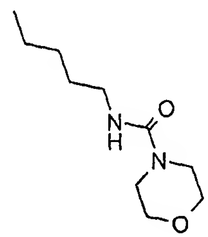
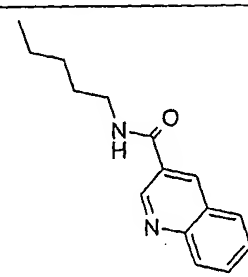
Boron tribromide (400 µL of 1 M in heptane) was added to a tube containing a chilled (0 °C) solution of a compound of Formula Xa (about 25 mg) in dichloromethane (1 mL). The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight at ambient temperature. The reaction mixture was diluted with methanol (1 mL) and hydrochloric acid (250 µL of 6 N), vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified by prep HPLC as described in Examples 8 – 72. Table 3 shows the structure of the starting material, a reference for the starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

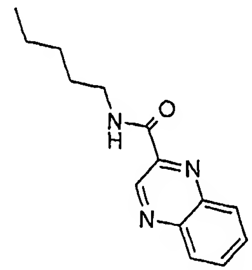
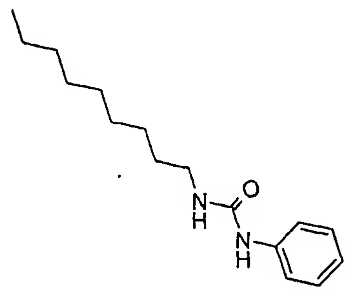
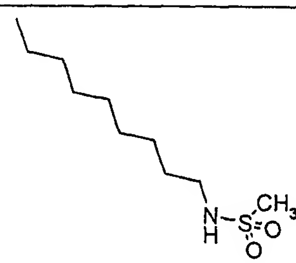
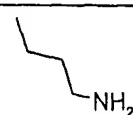
Table 3

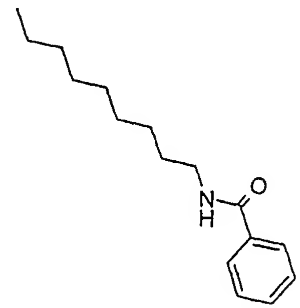
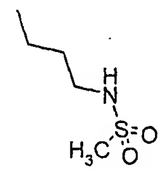
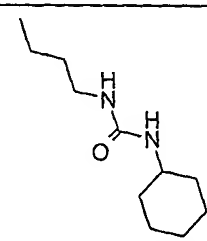
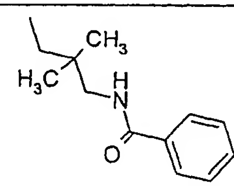


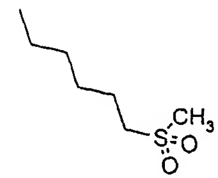
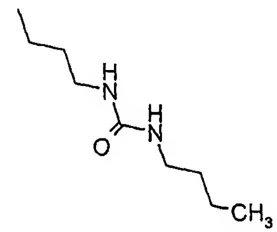
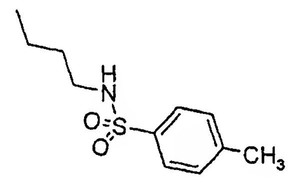
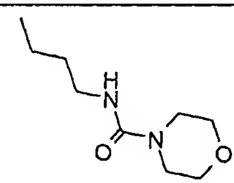
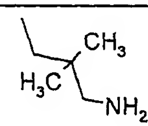
Xa → Ia

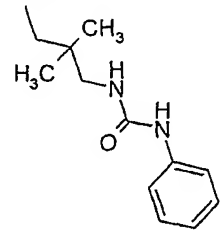
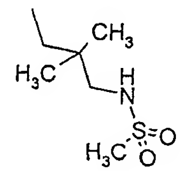
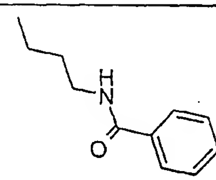
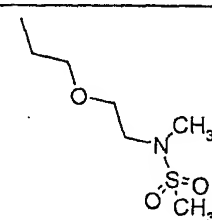
Example	Reference Formula Xa	R_1	Measured Mass (M+H)
111	U.S. Patent No. 6,756,382 Example 57		455.2222
112	U.S. Patent No. 6,331,539 Example 121		458.1657

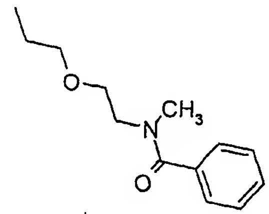
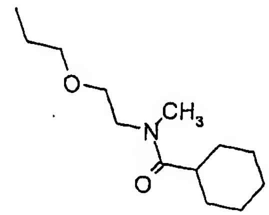
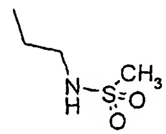
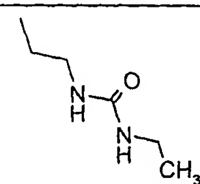
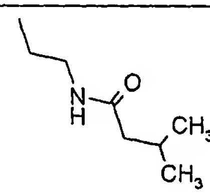
113	U.S. Patent No. 6,331,539 Example 111		378.1599
114	Example 3 Part C		300.1853
115	U.S. Patent No. 6,541,485 Example 121		413.2301
116	U.S. Patent No. 6,756,382 Example 182		455.2198

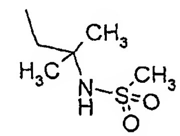
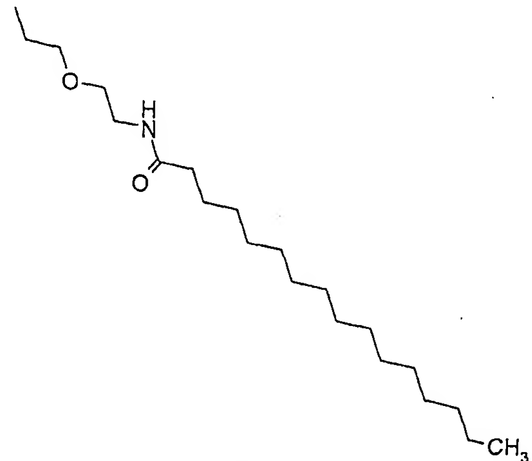
117	U.S. Patent No. 6,756,382 Example 183		456.2161
118	U.S. Patent No. 6,573,273 Example 145		475.2829
119	U.S. Patent No. 6,677,349 Example 243		434.2253
120	Example 73 Part A		286.1683

121	U.S. Patent No. 6,756,382 Example 187		460.2737
122	U.S. Patent No. 6,677,349 Example 247		364.1446
123	U.S. Patent No. 6,573,273 Example 158		411.2505
124	U.S. Patent No. 6,756,382 Example 190		418.2275

125	U.S. Patent No. 6,664,264 Example 16		377.1655
126	U.S. Patent No. 6,573,273 Example 162		385.2358
127	U.S. Patent No. 6,677,349 Example 253		440.1720
128	U.S. Patent No. 6,573,273 Example 163		399.2145
129	U.S. Patent No. 6,677,349#		314.1980

130	U.S. Patent No. 6,573,273 Example 169		433.2321
131	U.S. Patent No. 6,677,349 Example 256		392.1757
132	U.S. Patent No. 6,756,382 Example 196		390.1929
133	U.S. Patent No. 6,683,088 Example 3		408.1714

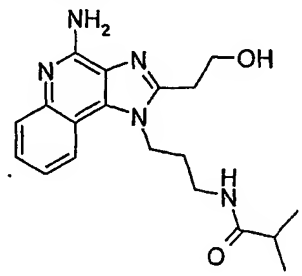
134	U.S. Patent No. 6,664,265 Example 8		434.2197
135	U.S. Patent No. 6,664,265 Example 73		440.2672
136	U.S. Patent No. 6,677,349#		350.1316
137	U.S. Patent No. 6,573,273#		343.1884
138	U.S. Patent No. 6,451,810#		356.2078

139	U.S. Patent No. 6,677,349[#]		378.1595
140	U.S. Patent Publication 2004/0091491 IRM3		554.4064

[#]Although not specifically exemplified the compound can be readily prepared using the disclosed synthetic routes.

Example 141

N-{3-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-2-methylpropionamide



Part A

1-(3-Aminopropyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine dihydrochloride (6 g, 16 mmol) was combined with triethylamine (11.2 mL, 80 mmol) and pyridine (100 mL). Isobutyryl chloride (1.9 g, 18 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was combined with saturated aqueous sodium bicarbonate and extracted with dichloromethane (3 x 200 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 6.2 g of crude *N*-{3-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}-2-methylpropionamide as a brown solid.

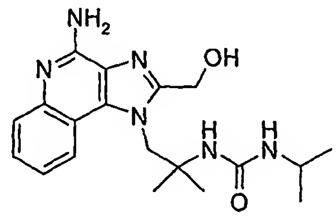
Part B

The material from Part A was combined with dichloromethane (40 mL), stirred until homogeneous, and then chilled in an ice bath. Boron tribromide (40 mL of 1 M in dichloromethane) was slowly added. The ice bath was removed and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was combined with methanol (50 mL) and hydrochloric acid (50 mL of 6 N) and heated at 50 °C for 2 hours. The solution was adjusted to pH 9 with sodium hydroxide (6 M) and then extracted first with ethyl acetate (3 x 100 mL) and then with dichloromethane. The organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure. The residue was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 0-10% methanol in dichloromethane), recrystallized from acetonitrile, and then dried in a vacuum oven to provide 208 mg of *N*-{3-[4-amino-2-(2-hydroxyethyl)-1*H*-

imidazo[4,5-*c*]quinolin-1-yl]propyl}-2-methylpropionamide as an off-white solid, mp 196-198 °C. Anal. calcd for $C_{19}H_{25}N_5O_2$: %C, 64.20; %H, 7.09; %N, 19.70; Found: %C, 63.99; %H, 7.28; %N, 19.63.

Example 142

1-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea



Part A

Under a nitrogen atmosphere, a solution of 1,2-diamino-2-methylpropane (52.20 mL, 503.3 mmol), triethylamine (131.8 mL, 958.8 mmol), and dichloromethane (1.0 L) was chilled in an ice water bath. 4-Chloro-3-nitroquinoline (100.0 g, 479.4 mmol) was added in portions over a period of 5 minutes. The reaction mixture was stirred at 0 °C for 2 hours and then allowed to slowly warm to ambient temperature. After 16 hours the reaction mixture was concentrated under reduced pressure. The residue was triturated with water (500 mL) for 1 hour. The resulting solid was isolated by filtration and dried overnight in a vacuum desiccator to provide 124.6 g of N^1-(3-nitroquinolin-1-yl)-2-methylpropane-1,2-diamine as a yellow crystalline solid.

Part B

Under a nitrogen atmosphere, a suspension of N^1-(3-nitroquinolin-1-yl)-2-methylpropane-1,2-diamine (60.0 g, 231 mmol) in dichloromethane (1.0 L) was chilled in an ice bath. Isopropyl isocyanate (23.8 mL, 242 mmol) was added dropwise over a period of 10 minutes. The reaction was allowed to slowly warm to room temperature. After 17 hours additional isopropyl isocyanate (about 2 mL) was added. After an additional 3 hours more isopropyl isocyanate (1 mL) was added. After 2 more hours the reaction mixture was concentrated under reduced pressure to provide 79.8 g of 1-{1,1-dimethyl-2-[(3-nitroquinolin-1-yl)amino]ethyl}-3-(1-methylethyl)urea as a bright yellow solid.

Part C

A pressure vessel was charged with the material from Part B, 5% Pt/C (4.24 g), and acetonitrile (1.5 L). The mixture was placed under hydrogen pressure for 20 hours and then filtered through a layer of CELITE filter aid. The filter cake was rinsed with additional acetonitrile. The filtrate was concentrated under reduced pressure. The residue was dissolved in toluene (750 mL) and then concentrated under reduced pressure to remove residual water. The toluene concentration was repeated. The residue was dissolved in dichloromethane (about 1 L), concentrated under reduced pressure, and then dried under high vacuum to provide 66.4 g of 1-{1,1-dimethyl-2-[(3-aminoquinolin-1-yl)amino]ethyl}-3-(1-methylethyl)urea as an orange foam.

Part D

Under a nitrogen atmosphere, a solution of 1-{1,1-dimethyl-2-[(3-aminoquinolin-1-yl)amino]ethyl}-3-(1-methylethyl)urea (66.0 g, 209 mmol) and triethylamine (32.1 mL, 230 mmol) in dichloromethane (1.0 L) was chilled in an ice bath. Ethoxyacetyl chloride (23.6 mL, 291 mmol) was added dropwise over a period of 10 minutes. The reaction mixture was allowed to slowly warm to ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was combined with 1-butanol (800 mL) and triethylamine (87 mL, 627 mmol) and heated at 140 °C for 3 hours. The reaction mixture was cooled to ambient temperature and then concentrated under reduced pressure to provide a light brown foam. This material was purified by column chromatography (silica gel, eluting with 98/2/0.5 chloroform/methanol/ammonium hydroxide) to provide 29.36 g of 1-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as a light yellow foam.

Part E

3-Chloroperoxybenzoic acid (26.33 g of 60%, 91.56 mmol) was added in portions over a period of 5 minutes to a chilled solution of the material from Part D in chloroform (350 mL). The reaction mixture was allowed to slowly warm to ambient temperature. After 2 hours the reaction mixture was chilled in an ice bath and ammonium hydroxide (100 mL) was added with vigorous stirring to homogenize. *Para*-toluenesulfonyl chloride (15.27 g, 80.12 mmol) was added in portions over a period of 10 minutes. The ice bath was removed and the reaction mixture was stirred for 30 minutes. The reaction mixture was diluted with water (100 mL) and chloroform (250 mL). The layers were separated.

The organic layer was washed with 10% sodium carbonate (200 mL) and water (200 mL). The combined aqueous was back extracted with chloroform (100 mL). The combined organics were washed with brine (200 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a light brown foam. The foam was purified by column chromatography (silica gel, eluting with 95/5 chloroform/methanol) and then recrystallized from acetonitrile to provide 3.75 g of 1-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as an off white solid.

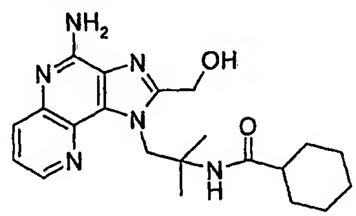
Part F

Under a nitrogen atmosphere, a suspension of 1-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea (1.19 g, 2.99 mmol) in dichloromethane (30 mL) was chilled in an ice bath. Boron tribromide (7.47 mL of 1 M in dichloromethane) was added. The reaction mixture was allowed to warm slowly to ambient temperature and then stirred for 18 hours. Additional boron tribromide (2 eq) was added. After 2 hours the reaction mixture was diluted with acetonitrile (10 mL) and the reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (10 mL) and acetonitrile (10 mL), stirred for an additional 16 hours, quenched with methanol (25 mL), and then concentrated under reduced pressure to provide an orange foam. The foam was dissolved in hydrochloric acid (25 mL of 6 N) and heated at 50 °C for 2 hours. The solution was neutralized with 50% sodium hydroxide. The resulting gummy precipitate was extracted with chloroform (3 x 15 mL). The combined organics were washed with brine (15 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide an off white solid. This material was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 15-50% CMA in chloroform) and then recrystallized from acetonitrile to provide 335 g of 1-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as a white crystalline solid, mp 196–199 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.38 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 7.5 Hz, 1 H), 7.43-7.38 (m, 1 H), 7.24-7.19 (m, 1 H), 6.54 (s, 2 H), 5.72 (s, 1 H), 5.63 (d, J = 7.6 Hz, 1 H), 5.46 (t, J = 5.7 Hz, 1 H), 5.01 (s, 2 H), 4.78 (s, 2 H), 3.78-3.67 (m, 1 H), 1.17 (bs, 6 H), 1.05 (d, J = 6.9 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.2, 154.2, 152.3, 145.6, 134.3, 126.8, 126.7, 121.5, 120.9, 115.8, 56.5, 54.2, 52.1, 26.4, 23.6; MS (APCI) *m/z* 371 $(M + H)^+$; Anal.

Calcd for $C_{19}H_{26}N_6O_2 \cdot 0.3H_2O$: %C, 60.72; %H, 7.13; %N, 22.36; Found: %C, 60.44; %H, 7.42; %N, 22.52.

Example 143

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide



Part A

1,2-Diamino-2-methylpropane (8.4 mL, 80.0 mmol) was added to a chilled (0 °C) solution of 4-chloro-3-nitro[1,5]naphthyridine (15.2 g, 72.7 mmol) and triethylamine (20.2 mL, 145 mmol) in dichloromethane (350 mL). The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was combined with water (300 mL) and heated at reflux with stirring for 1 hour. The reaction mixture was cooled and filtered. The isolated solid was washed with water and then dried under high vacuum to provide 18.5 g of N^1-(3-nitro[1,5]naphthyridin-4-yl)-2-methylpropane-1,2-diamine as a bright yellow powder.

Part B

Under a nitrogen atmosphere, a solution of sodium hydroxide (3.12 g, 78.0 mmol) in water (50 mL) was added to a solution of the material from Part A (18.5 g, 70.9 mmol) in tetrahydrofuran (200 mL). A solution of di-*tert*-butyl dicarbonate (17.0 g, 78.0 mmol) in tetrahydrofuran (100 mL) was added dropwise over a period of 30 minutes. Two (2) days later additional di-*tert*-butyl dicarbonate (2.0 g) was added. The reaction mixture was stirred for another 8 hours and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate (250 mL), washed sequentially with water (x2) and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was dissolved in warm 1/1 ethyl acetate/hexanes. The solution was allowed to slowly cool. The resulting precipitate was isolated by filtration and washed with hexanes to provide 17.7 g of *tert*-butyl *N*-{2-[(3-nitro[1,5]naphthyridin-4-yl)amino]-1,1-dimethylethyl}carbamate as a bright yellow crystalline solid.

Part C

A Parr vessel was charged with a solution of *tert*-butyl *N*-{2-[(3-nitro[1,5]naphthyridin-4-yl)amino]-1,1-dimethylethyl}carbamate (12.62 g, 34.9 mmol) in acetonitrile (100 mL) and 5% Pt/C (2.00 g). The vessel was placed under hydrogen pressure (50 psi, 3.4 X 10^5 Pa) until hydrogen uptake ceased. The reaction mixture was filtered through a layer of CELITE filter aid and the filter cake was rinsed with acetonitrile. The filtrate was concentrated under reduced pressure to provide 11.07 g of *tert*-butyl *N*-{2-[(3-amino[1,5]naphthyridin-4-yl)amino]-1,1-dimethylethyl]carbamate as a bright yellow foam.

Part D

Under a nitrogen atmosphere, a solution of the material from Part C (11.07 g, 33.4 mmol) in dichloromethane (330 mL) was cooled to 0 °C. Triethylamine (5.11 mL, 36.7 mmol) and ethoxyacetyl chloride (3.70 mL, 36.7 mmol) were added sequentially. The reaction mixture was stirred overnight while warming to ambient temperature and then concentrated under reduced pressure. The residue was dissolved in ethanol (300 mL). Triethylamine (16 mL) was added and the solution was heated at reflux under a nitrogen atmosphere over the weekend. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (250 mL), washed sequentially with water and brine, dried over magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (6 x 12 cm silica gel column eluting with ethyl acetate) to provide 11.5 g of a purple foam. This material was purified by flash chromatography (eluting with 2.5 % methanol in chloroform) to provide 10.07 g of *tert*-butyl *N*-[2-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]carbamate a purple foam.

Part E

3-Chloroperoxybenzoic acid (7.50 g of 57-86%) was added to a solution of the material from Part D in dichloromethane (250 mL). After 2.5 hours, additional 3-chloroperoxybenzoic acid (250 mg) was added and the reaction mixture was stirred for 1.5 hours. The reaction mixture was washed sequentially with 1% sodium carbonate (4 x 75 mL), water, and brine, dried over sodium sulfate, filtered, and then concentrated under

reduced pressure to provide 10.32 g of *tert*-butyl *N*-[2-(2-ethoxymethyl-5N-oxide-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]carbamate as a purple foam.

Part F

Concentrated ammonium hydroxide (20 mL) was added to a solution of the material from Part E (10.32 g, 24.9 mmol) in dichloromethane (200 mL). Toluenesulfonyl chloride (5.02 g, 26.3 mmol) was added in small portions over a period of 2 minutes. The reaction mixture was stirred for 2 hours and then diluted with water. The layers were separated. The organic layer was washed sequentially with 1% sodium carbonate (x3), water, and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (6 x 15 cm column of silica gel, eluting with 10% CMA in chloroform) to provide about 8 g of a purple foam. The foam was dissolved in ethanol, combined with activated charcoal (2 g), heated at reflux for 15 minutes, filtered, and then concentrated under reduced pressure to provide 7.59 g of *tert*-butyl *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]carbamate as a violet foam.

Part G

A solution of hydrochloric acid in ethanol (17 mL of 4.3 M) was added to a solution of the material from Part F in ethanol (100 mL). The reaction mixture was heated at 90 °C for 2 hours, allowed to cool, and then concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with chloroform (2 x 25 mL). The extracts were discarded. The aqueous was made basic with concentrated ammonium hydroxide and then extracted with chloroform (4 x 50 mL). The combined extracts were dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was crystallized from ethyl acetate/hexanes (about 100 mL). The solid was isolated by filtration, rinsed with cold 20% ethyl acetate in hexanes, and dried under vacuum. A second crop was obtained and combined with the first crop to provide 3.82 g of 1-(2-amino-2-methylpropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a gray crystalline solid.

Part H

Under a nitrogen atmosphere, a solution of 1-(2-amino-2-methylpropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (1.552 g, 4.94 mmol) in dichloromethane (50 mL) was cooled to 0 °C. Triethylamine (1.38 mL, 9.92 mmol) and

cyclohexylcarbonyl chloride (661 μL, 4.94 mmol) were added sequentially. Two (2) days later the reaction mixture was cooled and additional cyclohexylcarbonyl chloride (40 μL) was added. The reaction mixture was stirred overnight and then diluted with saturated sodium bicarbonate and dichloromethane (50 mL). The layers were separated. The organic layer was washed sequentially with water (x2) and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (4 x 13 cm silica gel column, eluting with 3% methanol in chloroform). The purified material was dissolved in refluxing propyl acetate (80 mL) with the aid of methanol, the methanol was boiled off, and the solution was allowed to slowly cool. The resulting precipitate was isolated by filtration, rinsed with cold propyl acetate, and dried under high vacuum at 70 °C to provide 1.37 g of *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide as a colorless crystalline solid, mp 210-211 °C. Anal. calcd for $C_{23}H_{32}N_6O_2$: %C, 65.07; %H, 7.60; %N, 19.80; Found: %C, 64.93; %H, 7.76; %N, 19.97.

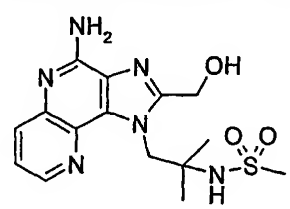
Part I

Boron tribromide (1.24 mL of 1 M in dichloromethane) was added dropwise to a chilled (ice bath) suspension of *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide (500 mg, 1.18 mmol) in dichloromethane (15 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred over the weekend. Additional boron tribromide (1 mL) was added and the reaction mixture was stirred for 24 hours. The reaction was quenched with methanol (10 mL) and then concentrated under reduced pressure. The residue was combined with hydrochloric acid (15 mL of 6 M), heated to 50 °C, and stirred for 2 hours. The resulting solution was cooled to ambient temperature and then neutralized (pH 7) with 10% sodium hydroxide. The resulting gummy precipitate was extracted with chloroform (3 x 15 mL). The combined extracts were washed with brine (15 mL), dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide an off white solid. This material was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 10-50% CMA in chloroform) to provide a white solid. The solid was triturated with hot acetonitrile, allowed to cool, isolated by filtration, and dried under vacuum to provide 233 mg of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-

imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide as a fine white solid, mp 230-232 °C; ^{1}H NMR (300 MHz, DMSO-d_6, 350 K) δ 8.53 (dd, J = 4.3, 1.6 Hz, 1 H), 7.95 (dd, J = 8.4, 1.5 Hz, 1 H), 7.87 (s, 1 H), 7.47 (dd, J = 8.4, 4.4 Hz, 1 H), 6.55 (s, 2 H), 5.31 (s, 1 H), 5.15 (s, 2 H), 4.79 (d, J = 5.4 Hz, 2 H), 1.90-1.80 (m, 1 H), 1.67-1.43 (m, 5 H), 1.31 (s, 6 H), 1.24-1.02 (m, 5 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.9, 154.6, 152.8, 142.8, 140.8, 134.2, 133.5, 133.3, 129.3, 122.5, 56.4, 55.0, 52.3, 44.9, 29.4, 25.7, 25.6, 24.9; MS (ESI) m/z 397 (M + H)$^+$; Anal. Calcd for $C_{21}H_{28}N_6O_2$: C, 63.62; H, 7.12; N, 21.20; Found: C, 63.77; H, 7.34; N, 21.50.

Example 144

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]methanesulfonamide



Part A

Under a nitrogen atmosphere, a solution of 1-(2-amino-2-methylpropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (1.588 g, 5.06 mmol) in dichloromethane (50 mL) was cooled to 0 °C. Triethylamine (1.41 mL, 10.12 mmol) and methanesulfonyl chloride (392 μL, 5.06 mmol) were added sequentially. The reaction mixture was allowed to slowly warm to ambient temperature overnight. Additional methanesulfonyl chloride (40 μL) was added and the reaction mixture was stirred at ambient temperature for an additional 5 hours. The reaction mixture was diluted with aqueous saturated sodium bicarbonate and the layers were separated. The organic layer was washed sequentially with water and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (4 x 15 cm silica gel column, eluting with a gradient of 5-7.5% methanol in chloroform). The purified material was dissolved in refluxing propyl acetate (80 mL) with the aid of methanol, the methanol was boiled off, and the solution was allowed to slowly cool. The resulting precipitate was isolated by filtration, rinsed with cold propyl acetate, and dried under high vacuum at 70 °C to provide 1.35 g of *N*-[2-(4-amino-2-ethoxoxymethyl-1*H*-

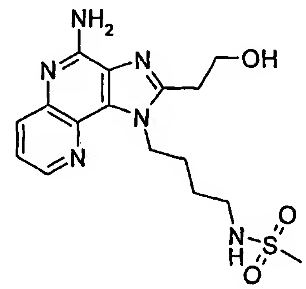
imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]methanesulfonamide as colorless needles, mp 209-210 °C. Anal. calcd for $C_{17}H_{24}N_6O_3S$: %C, 52.02; %H, 6.16; %N, 21.41; Found: %C, 52.09; %H, 6.35; %N, 21.60.

Part B

Boron tribromide (1.34 mL of 1 M in dichloromethane) was added dropwise to a chilled (ice bath) suspension of *N*-[2-(4-amino-2-ethoxoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]methanesulfonamide (500 mg, 1.27 mmol) in dichloromethane (15 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred over the weekend. Additional boron tribromide (1.5 mL) was added and the reaction mixture was stirred for 4 hours. Additional boron tribromide (1.5 mL) was added and the reaction mixture was stirred overnight. The reaction was quenched with methanol (15 mL) and then concentrated under reduced pressure. The residue was combined with hydrochloric acid (15 mL of 6 M), heated to 50 °C, and stirred for 2 hours. The resulting solution was cooled to ambient temperature and then neutralized (pH 7) with 10% sodium hydroxide. The resulting precipitate was isolated by filtration and rinsed with water to provide a white solid. This material was purified by prep HPLC (HORIZON HPFC system, eluting with a gradient of 10-50% CMA in chloroform) to provide a white solid. This material was recrystallized from acetonitrile and dried in a vacuum oven to provide 103 mg of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a white crystalline solid, mp 268–271 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (dd, J = 4.4, 1.6 Hz, 1 H), 7.95 (dd, J = 8.4, 1.5 Hz, 1 H), 7.90 (s, 1 H), 7.48 (dd, J = 8.4, 4.4 Hz, 1 H), 6.91 (s, 2 H), 5.62 (t, J = 5.9 Hz, 1 H), 5.10 (bs, 2 H), 4.92 (s, 2 H), 2.87 (s, 3 H), 1.35 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 152.3, 142.3, 140.3, 133.4, 133.1, 132.9, 128.8, 122.1, 57.2, 56.4, 54.3, 44.1, 25.1; MS (APCI) *m/z* 365 $(M + H)^+$; Anal. Calcd for $C_{15}H_{20}N_6O_3S$: C, 49.44; H, 5.53; N, 23.06; Found: C, 49.48; H, 5.40; N, 23.31.

Example 145

N-{4-{4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyl}methanesulfonamide



Part A

3-Methoxypropionyl chloride (2.7 g, 22 mmol) was added dropwise to a chilled (ice bath) solution of *tert*-butyl *N*-{4-[(3-amino[1,5]naphthyridin-4-yl)amino]butyl}carbamate 6.7 g, 20 mmol, U.S. Patent No.6,194,425, Example 42) in anhydrous pyridine (75 mL). The reaction mixture was heated at 120 °C overnight. The reaction was repeated on the same scale. The reaction mixtures were combined and concentrated under reduced pressure to provide 28 g of crude *tert*-butyl *N*-((4-{([3-(3-methoxypropionyl)amino[1,5]naphthyridin-4-yl]amino}butyl))carbamate as a red oil.

Part B

The crude material from Part A was dissolved in pyridine (150 mL). Pyridine hydrochloride (2.1 g) was added and the reaction mixture was heated at reflux overnight. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane and washed with brine. The aqueous layer was extracted with dichloromethane (x4). The combined organics were concentrated under reduced pressure. The residue was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-7% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 9.72 g of *tert*-butyl *N*-{4-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]buytl}carbamate as a brown glassy solid.

Part C

3-Chloroperoxybenzoic acid (7.8 g of 77%) was added in a single portion to a solution of *tert*-butyl *N*-{4-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]buytl}carbamate (7 g) in dichloroethane (100 mL). The reaction mixture was stirred at ambient temperature for 3 hours. Concentrated ammonium hydroxide (100 mL) was

added and the reaction mixture was stirred until a suspension formed. *Para*-toluenesulfonyl chloride (3.6 g) was added in a single portion. The reaction mixture was stirred at ambient temperature for 2 hours and then diluted with dichloromethane and brine. The organic layer was separated, washed with brine (x2), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 8.83 g of crude *tert*-butyl *N*-{4-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]buytl}carbamate as a brown solid.

Part D

The material from Part C was diluted with a small amount of dichloromethane and then hydrochloric acid in dioxane (126 mL of 4 M) was slowly added. The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure. The residue was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-7% methanol in dichloromethane containing 1% ammonium hydroxide) to provide 8 g of crude 1-(4-aminobutyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part E

Triethylamine (3.9 mL) was added to a solution of a portion (1.8 g) of the material from Part D in pyridine (20 mL). Methanesulfonyl chloride (485 μL) was added dropwise. The reaction mixture was stirred at ambient temperature for 2 hours, quenched with water (25 mL), and the stirred overnight. The reaction mixture was concentrated under reduced pressure and then diluted with dichloromethane. The organic layer was washed with brine (x2) and then concentrated under reduced pressure. The residue was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-5% methanol in dichloromethane containing 1% ammonium hydroxide for 5 minutes and then holding at 5%) to provide 400 mg of *N*-{4-{4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyl}methanesulfonamide.

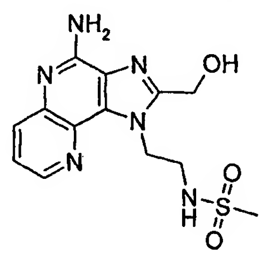
Part F

Boron tribromide (2.55 mL of 1 M in dichloromethane) was slowly added to a chilled mixture of the material from Part E in dichloromethane (10 mL). The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure. The residue was dissolved in methanol, combined with hydrochloric acid (50 mL of 6 M), heated at 50 °C for 2 hours, and concentrated under reduced pressure. The

residue was combined with a solution of ammonia in methanol (about 50 mL of 7 M) and then concentrated again. This procedure was repeated 3 times. The residue from the final concentration was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-10% methanol in dichloromethane containing 1% ammonium hydroxide for 10 minutes). The combined fractions were concentrated and then distributed onto solid phase extraction cartridges. The cartridges were eluted with ammonia in methanol (7 M). The resulting material was triturated with hot acetonitrile, cooled, isolated, and then dried in a vacuum oven to provide 111 mg of *N*-{4-{4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]butyl}methanesulfonamide, mp 194-195 °C. Anal. calcd for $C_{16}H_{22}N_6O_3S$: %C, 50.78; %H, 5.86; %N, 22.21; Found: %C, 50.83; %H, 6.12; %N, 21.70.

Example 146

N-[2-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethyl]methanesulfonamide



Part A

Methoxyacetyl chloride (5.9 g, 54 mmol) was added dropwise to a chilled (ice bath) solution of *tert*-butyl *N*-{2-[(3-amino[1,5]naphthyridin-4-yl)amino]ethyl}carbamate (15.0 g, 49.5 mmol, U.S. Patent No.6,194,425, Example 87) in anhydrous pyridine (100 mL). The reaction mixture was heated at reflux until analysis by liquid chromatography/mass spectroscopy (LCMS) indicated that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethanol (100 mL), combined with potassium carbonate solution (200 mL of 2 M), and heated at reflux for 4 hours. The reaction mixture was cooled and then concentrated under reduced pressure. The residue was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane. The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide

14 g of *tert*-butyl *N*-[2-(2-methoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethyl]carbamate.

Part B

Using the method of Example 145 Part C, the material from Part A was oxidized and then aminated to provide 17 g of crude *tert*-butyl *N*-[2-(4-amino-2-methoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethyl]carbamate as a sticky amber solid.

Part C

The material from Part B was dissolved in a mixture of dichloromethane (20 mL) and methanol (5 mL). Hydrochloric acid in dioxane (28 mL of 4 M) was added. More dichloromethane was added to facilitate stirring. The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure to provide crude 1-(2-aminoethyl)-2-methoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as an orange solid.

Part D

Triethylamine (35.6 mL) was added to a mixture of the material from Part C and pyridine (100 mL). The reaction mixture was cooled in an ice bath and then methanesulfonyl chloride (4.3 mL) was added dropwise. The reaction mixture was stirred at ambient temperature for 1 hour. Twice, more methanesulfonyl chloride (0.43 mL) was added and the reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane (x2). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 14 g of *N*-[2-(4-amino-2-methoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethyl]methanesulfonamide.

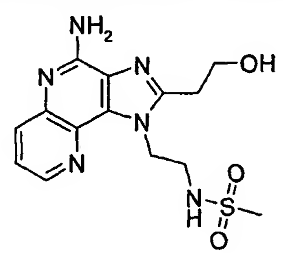
Part E

Boron tribromide (71.4 mL of 1 M in dichloromethane) was slowly added to a chilled (ice bath) mixture of the material from Part D in dichloromethane (50 mL). The reaction mixture was stirred at ambient temperature for 2 hours. Additional boron tribromide (0.5 eq) was added and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol, combined with hydrochloric acid (50 mL of 6 M), heated at 50 °C for 2 hours, and concentrated under reduced pressure. The residue was combined with

a solution of ammonia in methanol (about 40 mL of 7 M) and then concentrated again. This procedure was repeated 3 times. The residue from the final concentration was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-5% methanol in dichloromethane containing 1% ammonium hydroxide with a 10 minute ramp and a 20 minute hold, then with gradient of 6-10% methanol in dichloromethane containing 1% ammonium hydroxide with a 10 minute ramp and a 20 minute hold, and finally with gradient of 11-20% methanol in dichloromethane containing 1% ammonium hydroxide with a 10 minute ramp and a 20 minute hold) to provide 2.4 g of a brown solid. A small portion of this material was combined with hot acetonitrile containing a small amount of methanol, cooled, and then isolated by filtration. This procedure was carried out 3 times. After the final isolation the material was rinsed with ether and dried in a vacuum oven to provide 75 mg of *N*-[2-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethyl]methanesulfonamide as a beige solid, mp 239-242 °C. Anal. calcd for $C_{13}H_{16}N_6O_3S$: %C, 46.42; %H, 4.79; %N, 24.98; Found: %C, 46.35; %H, 4.70; %N, 24.70.

Example 147

N-{2-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}methanesulfonamide



Part A

Using the general method of Example 146 Part A, *tert*-butyl *N*-{2-[(3-amino[1,5]naphthyridin-4-yl)amino]ethyl}carbamate (17.0 g, 56.1 mmol) was reacted with 3-methoxypropionyl chloride (7.5 g, 61.7 mmol) to provide 9.0 g of crude product. Analysis by LCMS indicated that the crude product was about a 1:1 mixture of *tert*-butyl *N*-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}carbamate and 1-(2-aminoethyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine.

Part B

Triethylamine (13.8 mL) was added to a mixture of the material from Part A and dichloromethane (70 mL). The resulting solution was chilled in an ice bath. Di-*tert*-butyl dicarbonate (8.6 g) was added. The reaction mixture was stirred at ambient temperature for 2 hours and then quenched with water. The layers were separated. The organic layer was washed with sodium carbonate, dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 11 g of *tert*-butyl *N*-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}carbamate as a tan solid.

Part C

3-Chloroperoxybenzoic acid (13.2 g of 77%) was added in a single portion to a solution of the material from Part B (11 g, 29.6 mmol) in dichloroethane (50 mL). The reaction mixture was stirred at ambient temperature for 1.5 hours, then diluted with dichloromethane and washed with aqueous ammonium hydroxide (25 mL of concentrated ammonium hydroxide in 250 mL of water). The aqueous layer was extracted with dichloromethane. The combined organics were concentrated under reduced pressure. The residue was dissolved in dichloroethane (100 mL). Concentrated ammonium hydroxide (70 mL) was added and the reaction mixture was stirred until a suspension formed. *Para*-Toluenesulfonyl chloride (6.2 g, 32.5 mmol) was added in a single portion. The reaction mixture was stirred at ambient temperature for 1.5 hours, then diluted with aqueous sodium bicarbonate and extracted with dichloromethane (x3). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure. The residue was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-5% methanol in dichloromethane containing 1% ammonium hydroxide over 6 minutes and then holding at 5%) to provide 3.5 g of *tert*-butyl *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}carbamate as an orange solid.

Part D

A solution of hydrochloric acid in dioxane (58 mL of 4 M) was added to a solution of of *tert*-butyl *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}carbamate (3 g) in a small amount of dichloromethane/methanol. The reaction mixture was stirred overnight at ambient temperature and then concentrated under reduced

pressure to provide 3.7 g of crude 1-(2-aminoethyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine hydrochloride.

Part E

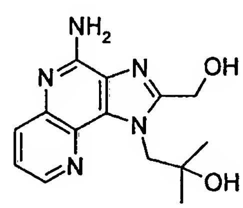
Using the general method of Example 146 Part D, a portion (1.1 g) of the material from Part D was reacted with methanesulfonyl chloride (322 µL) to provide 1.0 g of *N*-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}methanesulfonamide as a red solid.

Part F

Boron tribromide (7 mL of 1 M in dichloromethane) was slowly added to a chilled (ice bath) mixture of the material from Part E in dichloromethane (25 mL). The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure. The residue was dissolved in methanol, combined with hydrochloric acid (50 mL of 6 M), heated at 50 °C for 2 hours, and concentrated under reduced pressure. The residue was combined with a solution of ammonia in methanol (about 30 mL of 7 M) and then concentrated again. This procedure was repeated 3 times. The residue from the final concentration was purified by prep HPLC (COMBIFLASH system eluting with a gradient of 0-10% methanol in dichloromethane containing 1% ammonium hydroxide). The residue was combined with hot acetonitrile, cooled, and the acetonitrile was decanted off. This procedure was carried out 3 times. The material was isolated by filtration, rinsed with ether and dried in a vacuum oven to provide 950 mg of *N*-{2-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]ethyl}methanesulfonamide, mp 136-138 °C. Anal. calcd for $C_{14}H_{18}N_6O_3S$: %C, 47.99; %H, 5.18; %N, 23.98; Found: %C, 47.69; %H, 5.36; %N, 23.77.

Example 148

1-(4-Amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol



Part A

Under a nitrogen atmosphere, 1-amino-2-methylpropan-2-ol (25.5 g, 0.28 mol) was added over a period of 30 minutes to a solution of 4-chloro-3-nitro[1,5]naphthyridine (54.5 g, 0.26 mol) in dichloromethane (1 L). A water bath was used to control the exotherm and maintain the temperature of the reaction at or below 27 °C. The reaction mixture was stirred at ambient temperature overnight. The resulting precipitate (crop 1) was isolated by filtration. The filtrate was concentrated under reduced pressure to provide crop 2. The two crops were slurried separately with de-ionized water for 2 hours and then isolated by filtration. Crop 1: 40.53 g of 2-methyl-2-[(3-nitro[1,5]naphthyridin-4-yl)amino]propan-2-ol as a yellow solid. Crop 2: tan solid. Crop 2 was dissolved in dichloromethane and loaded onto an alumina column. The column was eluted first with 1% methanol in dichloromethane and then with acetone. The combined eluents were concentrated under reduced pressure. The residue was recrystallized from ethanol (10 mL/g) to provide 6.95 g of 2-methyl-1-[(3-nitro[1,5]naphthyridin-4-yl)amino]propan-2-ol.

Part B

A Parr vessel was charged with 2-methyl-1-[(3-nitro[1,5]naphthyridin-4-yl)amino]propan-2-ol (44.12 g, 0.17 mol), 5% Pt/C (4.4 g) and isopropyl alcohol (890 mL). The vessel was placed under hydrogen pressure (35 psi, 2.4 x 10^5 Pa) until hydrogen uptake ceased. The reaction mixture was filtered through a layer of filter aid. The filter cake was rinsed with additional isopropyl alcohol. The filtrate was concentrated under reduced pressure to provide 1-[(3-amino[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a thick oil.

Part C

Under a nitrogen atmosphere, ethoxyacetyl chloride (19.1 g, 0.156 mol) was added over a period of 12 minutes to a mixture of 1-[(3-amino[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (28.95 g, 0.125 mol) in pyridine (300 mL). The reaction mixture was stirred at ambient temperature for 4 hours and then at reflux for 4 hours. The reaction mixture was allowed to cool to ambient temperature overnight and then concentrated under high vacuum. The residue was dissolved in 5% potassium carbonate (200 mL) and then extracted with dichloromethane (200 mL). The extract was filtered to remove some insoluble material, dried over magnesium sulfate, filtered, and then concentrated under high vacuum. The residue was dissolved in dichloromethane (150 mL) and eluted through

a short column of alumina. The eluent was concentrated under reduced pressure and air dried to provide 31.9 g of 1-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol.

Part D

A flask containing a solution of 1-(2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol (29.94 g, 83 mmol) in dichloromethane (300 mL) was covered with aluminum foil. 3-Chloroperoxybenzoic acid (28.65 g of 50%) was added in portions over a period of 50 minutes. The reaction mixture was stirred for an additional 40 minutes, then diluted with 5% aqueous potassium carbonate and stirred. The organic layer was separated, washed with brine (100 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a yellow paste. This material was combined with ether (100 mL) and stirred overnight. The resulting solid was isolated by filtration to provide 11.84 g of 1-(2-ethoxymethyl-5-oxo-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol. The aqueous potassium carbonate layer was partially concentrated, saturated with additional potassium carbonate, and then extracted with dichloromethane. The extract was dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 15.23 g of a dark oil. The oil was combined with ether (100 mL) and stirred overnight. The resulting solid was isolated by filtration to provide 11.51 g of 1-(2-ethoxymethyl-5-oxo-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol.

Part E

Concentrated ammonium hydroxide (241 mL) was added to a solution of 1-(2-ethoxymethyl-5-oxo-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol (23.35 g, 74 mmol) in dichloromethane (300 mL). A solution of *para*-toluenesulfonyl chloride (15.52 g, 81 mmol) in dichloromethane (50 mL) was added with rapid stirring over a period of 25 minutes. The reaction mixture was stirred overnight. Concentrated ammonium hydroxide (25 mL) and a solution of *para*-toluenesulfonyl chloride (2 g) in dichloromethane (10 mL) was added and the reaction mixture was stirred for 5 hours. The organic phase was separated, washed with a solution of potassium carbonate (16 g) in water (300 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 30.17 g of crude product. This material was combined with acetonitrile (300 mL), stirred, heated to reflux, and then allowed to cool with stirring to

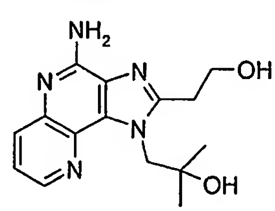
ambient temperature. The resulting solid was isolated by filtration and then dried at 75 °C under vacuum to provide 14.4 g of a solid. This material was recrystallized from ethyl acetate (17.5 mL/g), isolated by filtration, and then dried under vacuum at 75 °C for 22 hours to provide 12.29 g of 1-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol as an off white solid, mp 157-159 °C. Anal. calcd for $C_{16}H_{21}N_5O_2$: %C, 60.94; %H, 6.71; %N, 22.21; Found: %C, 61.06; %H, 6.67; %N, 22.37.

Part F

A solution of boron tribromide in dichloromethane (11.8 mL of 1 M) was added to a chilled (0 °C) suspension of 1-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol hydrobromide (1.24 g, 3.93 mmol) in dichloromethane (30 mL). The reaction mixture was allowed to come to ambient temperature with stirring for 16 hours. Methanol (15 mL) and hydrochloric acid (10 mL of 6 N) were added and the reaction mixture was heated at reflux for 2.5 hours. The reaction mixture was made basic with sodium hydroxide and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed sequentially with water and brine, dried over magnesium sulfate, and then concentrated under reduced pressure to provide a white solid. This material was crystallized from ethyl acetate and then dried under vacuum at 95 °C for 16 hours to provide 0.55 g of 1-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol as a white powder, mp 235-237 °C. Anal. calcd for $C_{14}H_{17}N_5O_2$: %C, 58.52; %H, 5,96; %N, 24.37; Found: %C, 58.40; %H, 5.82; %N, 24.45.

Example 149

1-[4-Amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol



Part A

A mixture of triethyl orthoformate (10 mL, 60.1 mmol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (40.9 g, 0.23 mol) (Meldrum's acid) was heated at 92 °C for 90 minutes and then cooled to 70 °C over one hour. 3-Amino-5-bromopyridine (40.9 g, 0.20 mol) was slowly added over 10 minutes with an ethanol rinse while maintaining the reaction temperature between 60 and 70 °C. The reaction was then heated for an additional 20 minutes and allowed to cool to room temperature. The reaction mixture was filtered and washed with ethanol (150 mL) yielding a tan solid. The solid was dried under vacuum for 2 hours to yield 59.14 g of 5-{[(5-bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione as a light yellow crystalline solid, mp 200-202 °C.

Part B

5-{[(5-Bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (59 g, 0.18 mol) was slowly added to DOWTHERM A heat transfer fluid (2000 mL) over a period of 5 minutes at 235-238 °C. Following addition, the reaction was maintained for an additional 5 minutes and then allowed to cool to 40 °C. A brown precipitate formed, which was filtered and washed with hexanes (150 mL). The brown solid was suspended in an ethanol/water mixture (90:10, 1500 mL), heated to a boil for 30 minutes, isolated by filtration, and washed with ethanol (200 mL) to yield 30.8 g of 7-bromo[1,5]naphthyridin-4-ol as a dark brown powder.

Part C

A mixture of 7-bromo[1,5]naphthyridin-4-ol (33 g, 0.147 mol) and fuming nitric acid (350 mL) was heated at reflux (90 °C internal reaction vessel temperature) for 3 hours. The reaction mixture was cooled to 50 °C, poured over 1 L of ice and neutralized to pH 2-3 with a solution of 50% aqueous sodium hydroxide. The resulting precipitate was filtered, washed with water, and dried over vacuum for 3 days to yield 25.1 g of 7-bromo-3-nitro[1,5]naphthyridin-4-ol as a yellow crystalline solid.

Part D

Phosphorous oxychloride (16.76 g, 10.19 mL, 109.3 mmol) was added slowly dropwise to a suspension of 7-bromo-3-nitro[1,5]naphthyridin-4-ol (21.09 g, 78.1 mmol) in *N,N*-dimethylformamide (250 mL) (DMF) at ambient temperature and maintained overnight. The reaction mixture was then added to ice water (400 mL) with stirring. A solid precipitate formed, which was isolated by vacuum filtration and washed with water.

The material was dried under high vacuum at ambient temperature overnight to yield 20.79 g of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine as a tan solid.

Part E

Triethylamine (35.95 mL, 257.9 mmol) was added to a suspension of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (49.6 g, 172 mmol) in dichloromethane (500 mL). 1-Amino-2-methylpropan-2-ol (16.86 g, 189 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 16 hours and then concentrated under reduced pressure. The residue was triturated with water and stirred for 1 hour. The precipitated solid was isolated by filtration, washed with water, and dried. This material was suspended in diethyl ether (400 mL), sonicated, isolated by filtration, and then dried in a vacuum oven at 40 °C for 16 hours to provide 58.1 g of 1-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a yellow solid, mp 189-190 °C.

Part F

A Parr vessel was charged with 5% Pt/C (5.8 g) and a suspension of 1-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (58.00 g) in acetonitrile (800 mL) and methanol (400 mL). The vessel was placed under hydrogen pressure (30 psi, 2.1 X 10^5 Pa) for 8 hours. The reaction mixture was filtered through a layer of CELITE filter aid. The filtrate was concentrated under reduced pressure to provide 52.70 g of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol as a yellow foam.

Part G

3-Methoxypropionyl chloride (24.90 g, 203 mmol) was added over a period of 5 minutes to a mixture of 1-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]-2-methylpropan-2-ol (52.70 g, 169 mmol), chloroform (100 mL), and acetonitrile (530 mL). The reaction mixture was stirred at ambient temperature overnight. The precipitated solid was isolated by filtration, washed well with acetonitrile, and then dried to provide 60.10 g of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-3-methoxypropionamide hydrochloride as a brown solid, mp 206-208 °C.

Part H

A mixture of *N*-{7-bromo-4-[(2-hydroxy-2-methylpropyl)amino][1,5]naphthyridin-3-yl}-3-methoxypropionamide hydrochloride (60.00 g, 138 mmol), potassium carbonate (60 g), water (300 mL), and ethanol (900 mL) was heated at reflux for 16 hours and then

concentrated under reduced pressure. The precipitated solid was isolated by filtration, washed sequentially with water and methanol, and dried to provide a brown solid. This material was dissolved in a 3/1 mixture of chloroform/methanol and decolorized with activated charcoal to provide 38.5 g of 1-[7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a white solid, mp 125 °C. Anal. calcd for $C_{16}H_{19}BrN_4O_2$: %C, 50.67; %H, 5.05; %N, 14.77; Found: %C, 50.86; %H 4.94; %N, 15.01.

Part I

3-Chloroperoxybenzoic acid (34.77 g of 75%, 151 mmol) was added to a solution of 1-[7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (38.2 g, 101 mmol) in dichloromethane (450 mL) and the reaction mixture was stirred for 3 hours. The reaction mixture was diluted with dichloromethane (200 mL), washed sequentially with 4% aqueous sodium carbonate (2 x 150 mL) and brine (1 x 150 mL), and concentrated under reduced pressure to provide the N-oxide derivative. The N-oxide derivative was combined with dichloromethane (450 mL) and concentrated ammonium hydroxide (200 mL) and the mixture was cooled in an ice bath. *Para*-Toluenesulfonyl chloride (24 g) was added in portions. After the addition was complete the ice bath was removed and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with dichloromethane (200 mL). Suspended solids were isolated by filtration, washed with water, and dried to provide 7.60 g of 1-[4-amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as an off white solid, mp 210-211 °C. Anal. calcd for $C_{16}H_{20}BrN_5O_2$: %C, 48.74; %H, 5.11; %N, 17.76; Found: %C, 48.63; %H, 5.10; %N, 17.80.

Part J

A Parr vessel was charged with 10 % Pd/C (0.6 g) and a suspension of 1-[4-amino-7-bromo-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol (4.0 g) in acetonitrile (150 mL) and methanol (50 mL). The vessel was placed under hydrogen pressure (50 psi, 3.4 X 10^5 Pa) for 3 hours. The reaction mixture was diluted with 1/1 chloroform/methanol (100 mL), filtered through a layer of CELITE filter aid, and concentrated under reduced pressure. The residue was triturated with acetonitrile to provide 3.55 g of 1-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol hydrobromide as a white powder, mp 234-235 °C. Anal. calcd

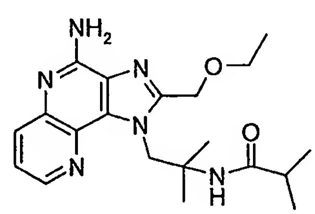
for $C_{16}H_{22}BrN_5O_2$: %C, 48.49; %H, 5.60; %N, 17.67; Found: %C, 48.64; %H, 5.69; %N, 17.62.

Part K

A solution of boron tribromide in dichloromethane (22.71 mL of 1 M) was added to a chilled (0 °C) suspension of 1-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol hydrobromide (3.00 g, 7.57 mmol) in dichloromethane (100 mL). The reaction mixture was allowed to come to ambient temperature with stirring for 16 hours. Methanol (30 mL) and hydrochloric acid (30 mL of 6 N) were added and the reaction mixture was heated at reflux for 2.5 hours. The reaction mixture was made basic with sodium hydroxide and the layers were separated. The aqueous layer was extracted with dichloromethane (100 mL). The extract was washed sequentially with water and brine, dried over magnesium sulfate, and then concentrated under reduced pressure to provide a pink solid. This material was crystallized from acetonitrile to provide 0.68 g of 1-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol. The aqueous layer was combined with the water and brine washings and allowed to stand overnight. A precipitate was isolated by filtration, washed with water, and dried under vacuum at 95 °C for 3 hours to provide 1.16 g of 1-[4-amino-2-(2-hydroxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol as a pink crystalline solid, mp 194-195 °C. Anal. calcd for $C_{15}H_{19}N_5O_2$: %C, 59.79; %H, 6.36; %N, 23.24; Found: %C, 59.51; %H, 6.59; %N, 23.34.

Examples 150 – 155

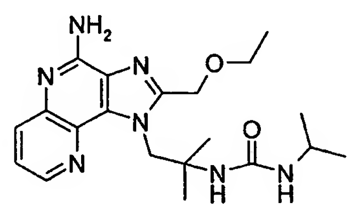
Preparation of *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]-2-methylpropionamide



Triethylamine (556 μL, 4.00 mmol) and isobutyryl chloride (230 μL, 2.20 mmol) were added sequentially to a chilled (0 °C) solution of 1-(2-amino-2-methylpropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (628 mg, 2.00 mmol) in

dichloromethane (20 mL). The reaction mixture was allowed to warm slowly to ambient temperature overnight. The reaction mixture was quenched with aqueous saturated sodium bicarbonate and diluted with dichloromethane (50 mL). The organic layer was separated, washed sequentially with water and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to an amber foam. This material was dissolved in hot propyl acetate (10 mL) and then allowed to cool overnight. Hexanes were added and the now cloudy solution was heated until clear and then allowed stand until crystals formed. The solvent was removed by pipette. The crystals were rinsed with cold propyl acetate/hexanes and then dried under high vacuum at 70 °C to provide 464 mg of *N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]-2-methylpropionamide as an off white crystalline solid, mp 154.5-155.5 °C. Anal. calcd for $C_{20}H_{28}N_6O_2$: %C, 62.48; %H, 7.34; %N, 21.86; Found: %C, 62.14; %H, 7.62; %N, 21.71.

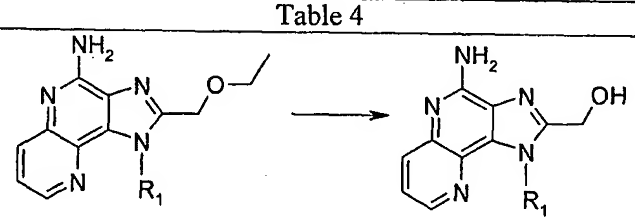
Preparation of 1-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea



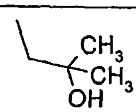
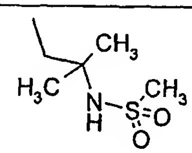
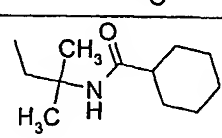
Under a nitrogen atmosphere, isopropyl isocyanate (206 µL, 2.10 mmol) was added to a chilled (0 °C) solution of 1-(2-amino-2-methylpropyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (628 mg, 2.00 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to warm slowly to ambient temperature overnight. The resulting precipitate was isolated by filtration and then dried under vacuum at 70 °C to provide 669 mg of 1-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]-3-(1-methylethyl)urea as white powder, mp 172.5-173.5 °C. Anal. calcd for $C_{20}H_{29}N_7O_2$: %C, 60.13; %H, 7.32; %N, 24.54; Found: %C, 59.88; %H, 7.55; %N, 24.51.

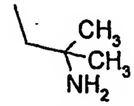
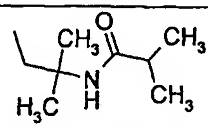
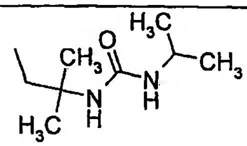
A solution of boron tribromide in dichloromethane (about 4 eq of 1 M) was added to a tube containing a chilled (0 °C) solution of a compound of Formula Xb (25 mg, 1 eq) in dichloromethane (1 mL). The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight at ambient temperature. The reaction mixture was diluted with methanol (1 mL) and hydrochloric acid (500 µL of 6 N), vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. Table 4 shows the structure of the starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Table 4



Xb → Ia

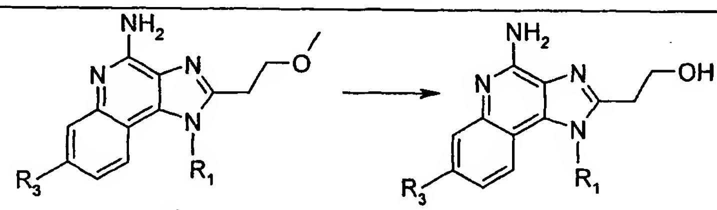
Example	R_1	Measured Mass (M+H)
150		288.1440
151		365.1378
152		397.2348

153		287.1607
154		357.2055
155		372.2157

Examples 156 – 161

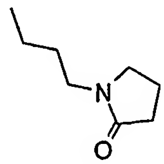
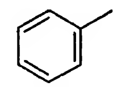
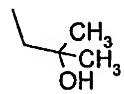
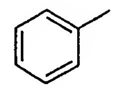
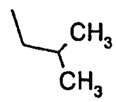
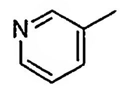
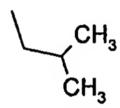
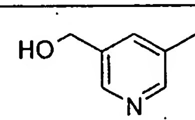
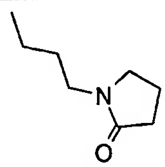
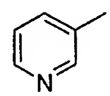
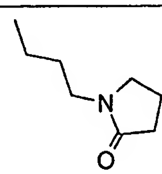
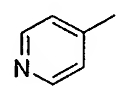
A solution of boron tribromide in heptane (400 µL of 1 M) was added to a tube containing a chilled (0 °C) solution of a compound of Formula Xc (about 25 mg) in dichloromethane (1 mL). The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight at ambient temperature. The reaction mixture was diluted with methanol (1 mL) and hydrochloric acid (250 µL of 6 N), vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. Table 5 shows the structure of the starting material, a reference for the starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Table 5



Xc → Ia

Example	Reference Formula Xc	R_1	R_3	Measured Mass (M+H)

156	U.S. Patent Publication 2004/0147543 Example 206			430.2227
157	U.S. Patent Publication 2004/0147543 Example 136			377.1985
158	U.S. Patent Publication 2004/0147543 Example 145			362.2008
159	U.S. Patent Publication 2004/0147543 Example 146			392.2104
160	U.S. Patent Publication 2004/0147543 Example 183			431.2209
161	U.S. Patent Publication 2004/0147543 Example 184			431.2220

Examples 162 – 186

Part A

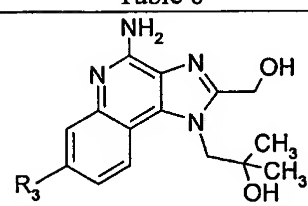
1-(4-Amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (2 g, U.S. Patent Publication 2004/0147543 Example 125) was dissolved in 7:3 volume:volume chloroform:methanol (100 mL). Aliquots (2 mL, 1.0 eq.) were added to test tubes and the solvent was removed by vacuum centrifugation. A tube was charged with a boronic acid (1.1 eq) from the table below. *n*-Propanol (1.6 mL) was added to each tube, the tube was purged with nitrogen, and then sonicated until the contents were well mixed. Each tube was then charged sequentially with 150 µL of a solution of palladium (II) acetate in toluene (60 mg of palladium (II) acetate dissolved in 15 mL of toluene), 600 µL of 2 M aqueous sodium carbonate solution, 113 µL of water, and 53 µL of a 15 mole % solution of triphenylphosphine in *n*-propanol. The tubes were purged with nitrogen and then heated at 80 °C overnight.

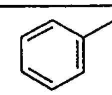
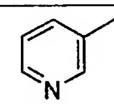
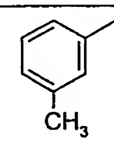
The reaction mixtures were purified by solid phase extraction. Sufficient hydrochloric acid (1 N) was added to each reaction mixture to adjust the pH to <5. Each reaction mixture was loaded onto a cartridge (Waters Oasis Samples Extraction Cartridges MCX 6cc). Methanol (5 mL) was added to each cartridge. The cartridge was placed in a clean test tube. The cartridge was eluted with two successive 5 mL portions of 1 N ammonia in methanol. The solvent was removed by vacuum centrifugation.

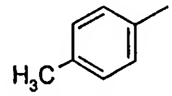
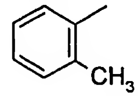
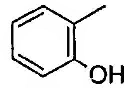
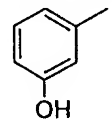
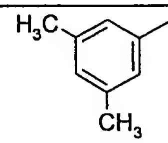
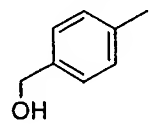
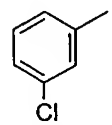
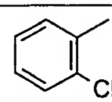
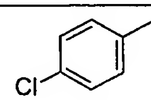
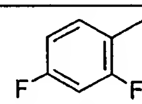
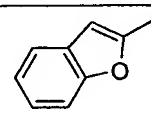
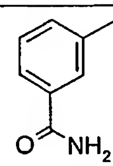
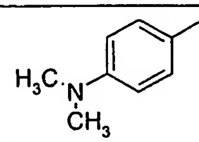
Part B

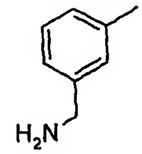
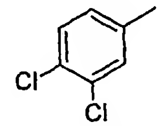
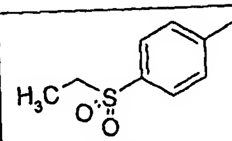
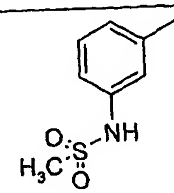
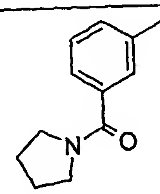
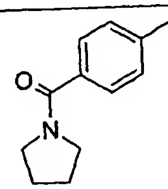
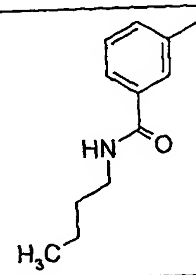
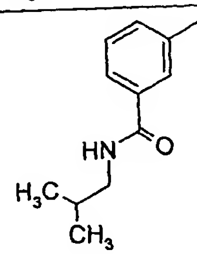
Dichloromethane (1 mL) was added to each tube, the tube was sonicated to dissolve the solids, and then the tube was chilled to 0 °C in an ice bath. A solution of boron tribromide in heptane (600 µL of 1 M) was added to each tube. The tube was vortexed, maintained at 0 °C for 0.5 hour, and then shaken overnight at ambient temperature. The solvents were removed by vacuum centrifugation. Methanol (1 mL) and hydrochloric acid (1 mL of 6 N) were added to each tube, the tubes were vortexed, and then the solvents were removed by vacuum centrifugation. The compounds were purified as described above for Examples 156 – 161. Table 6 shows the boronic acid, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

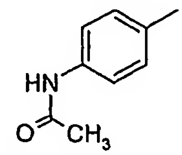
Table 6



Example	Reagent	R_3	Measured Mass (M+H)
162	Phenylboronic acid		363.1847
163	Pyridine-3-boronic acid		364.1779
164	3-Methylphenylboronic acid		377.2001

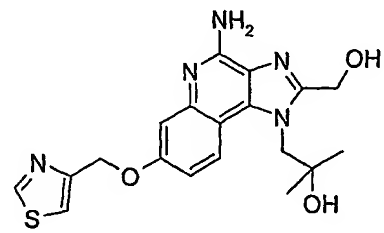
165	4-Methylphenylboronic acid		377.1979
166	*o*-Tolylboronic acid		377.1990
167	(2-Hydroxyphenyl)boronic acid		379.1776
168	3-Hydroxyphenylboronic acid		379.1755
169	3,5-Dimethylphenylboronic acid		391.2130
170	4-(Hydroxymethyl)phenylboronic acid		393.1935
171	3-Chlorophenylboronic acid		397.1432
172	2-Chlorophenylboronic acid		397.1447
173	4-Chlorophenylboronic acid		397.1431
174	2,4-Difluorophenylboronic acid		399.1642
175	Benzo[b]furan-2-boronic acid		403.1812
176	(3-Aminocarbonylphenyl)boronic acid		406.1889
177	4-(*N*,*N*-Dimethylamino)phenylboronic acid		406.2255

178	(3-Aminomethylphenyl)boronic acid hydrochloride		392.2108
179	3,4-Dichlorophenylboronic acid		431.1061
180	4-(Ethylsulfonyl)phenylboronic acid		455.1771
181	3-(Methylsulfonylamino)phenylboronic acid		456.1727
182	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		460.2364
183	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		460.2395
184	3-(Butylaminocarbonyl)phenylboronic acid		462.2488
185	3-(Isobutylaminocarbonyl)phenylboronic acid		462.2527

186	4'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)acetanilinde		420.2022

Example 187

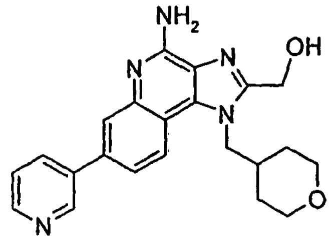
1-[4-Amino-2-hydroxymethyl-7-(thiazol-4ylmethoxy)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol



Under a nitrogen atmosphere, a solution of 1-[4-amino-2-ethoxymethyl-7-(thiazol-4ylmethoxy)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (400 mg, 0.94 mmol, which can be prepared as described in International Application No. PCT/US04/28021 Example 137) in dichloromethane (50 mL) was cooled to 0 °C in an ice bath. A solution of boron tribromide in dichloromethane (3.76 mL of 1.0 M) was added slowly. The reaction mixture was allowed to slowly warm to ambient temperature overnight. The reaction mixture was diluted with hydrochloric acid (20 mL of 6 N) and stirred for 30 minutes. The layers were separated. The organic layer was washed with 6 N hydrochloric acid (3 x 20 mL) and then discarded. The aqueous layer was made basic by the addition of solid potassium carbonate. A precipitate was isolated by filtration, dissolved in hot chloroform, and then purified by prep HPLC (HORIZON HPFC system eluting with 0 – 10% CMA in chloroform over 192 mL and then with 10-40% CMA in chloroform over 1400 mL) to provide a solid. This material was crystallized from acetonitrile to provide 181 mg of 1-[4-amino-2-hydroxymethyl-7-(thiazol-4ylmethoxy)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a white solid, mp 260-262 °C. Anal. calcd for $C_{19}H_{21}N_5O_3S$: %C, 56.81; %H, 5.41; %N, 17.26; Found: %C, 56.82; %H, 5.54; %N, 17.23.

Example 188

[4-Amino-7-pyridin-3-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol



Part A

To a mixture of 1-tetrahydro-2*H*-pyran-4-ylmethanamine HCl (19 g, 120 mmol), dichloromethane (626 mL), and triethyl amine (43.7 mL, 313 mmol) was added 4-chloro-3-nitroquinoline at 0 °C. The resulting bright yellow solution was stirred at ambient temperature for 18 hours. The reaction was then concentrated under reduced pressure. The resulting solid was stirred in water (100 mL) and filtered to give 43 g of 7-bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a yellow powder.

Part B

7-Bromo-3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (20 g, 55 mmol) was dissolved in a mixture of acetonitrile (500 mL) and isopropyl alcohol (50 mL) and the solution was placed in a pressure bottle. Platinum on carbon (5%, 2 g) was then added and the reaction mixture was shaken under H_2 at 48 PSI (3.3 x 10^5 Pa). After 2 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give 7-bromo-N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine which was carried forward without further purification assuming quantitative yield.

Part C

Chloroacetyl chloride (5.2 mL, 65 mmol) was added to 7-bromo-N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (55 mmol) dissolved in 273 mL of dichloromethane at 0 °C. A solid formed after adding half of the chloroacetyl chloride at which point additional dichloromethane (100 mL) was added. The reaction was stirred for 1 hour at ambient temperature. The yellow suspension was quenched first with aqueous saturated sodium bicarbonate followed by 50% aqueous sodium hydroxide until a pH of 14 was reached. Filtration provided 10 g of *N*-{7-bromo-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]quinolin-3-yl}-2-chloroacetamide as a tan solid. The filtrate was placed in a separatory funnel and the layers were separated. The aqueous layer was extracted with additional dichloromethane. The combined organic extracts were combined, dried over

sodium sulfate, filtered, and concentrated under reduced pressure to afford additional *N*-{7-bromo-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]quinolin-3-yl}-2-chloroacetamide as a yellow oil. The yellow oil was carried forward without further purification assuming a 50% yield (27.3 mmol). The oil was combined with ethanol (100 mL) and triethylamine (7.5 mL, 54 mmol). The resulting yellow solution was refluxed for 2 hours. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure to provide 7-bromo-2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a brown oil that was used without further purification assuming quantitative yield.

Part D

Potassium acetate (5.3 g, 55 mmol) was added to 7-bromo-2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (27.3 mmol) dissolved in dimethylformamide (100 mL). The resulting suspension was stirred at 90 °C for 1 hour. The reaction was cooled to ambient temperature and water (200 mL) was added. The aqueous layer was extracted with chloroform. The combined organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford an orange oily solid. Chromatography (SiO_2, 0-30% 80/18/2 v/v/v $CHCl_3$/CH_3OH/concentrated NH_4OH (CMA)/$CHCl_3$) gave material that was stirred in acetonitrile and filtered to provide 2.3 g of [7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl acetate as a tan solid.

Part E

3-Chloroperoxybenozic acid (2.4 g, 50% pure, 7.0 mmol) was added to a mixture of [7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl acetate (2.3 g, 5.4 mmol) and chloroform (27 mL) at ambient temperature. The reaction was stirred at this temperature for 18 hours. Saturated aqueous sodium bicarbonate (50 mL) and water (50 mL) were then added to the reaction and the layers were separated. The aqueous layer was extracted with additional dichloromethane. The organic layers were combined, dried over sodium sulfate, and concentrated under reduced pressure to a dark oil. This oil was dissolved in methanol (27 mL) and to this solution was added 15 M ammonium hydroxide (3.6 mL, 54 mmol) and benzene sulfonyl chloride (2.9 mL, 23 mmol). The resulting reaction mixture was stirred at ambient temperature for 2 hours before adding additional 15 M ammonium hydroxide (3.6 mL, 54 mmol) and benzene

sulfonyl chloride (2.9 mL, 23 mmol). The reaction was stirred 18 hours. The reaction was then concentrated under reduced pressure and diluted with saturated aqueous sodium bicarbonate and chloroform. A suspension resulted that was filtered to afford a solid that was stirred with saturated aqueous sodium bicarbonate and filtered to give 1.1 g of [4-amino-7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as a white solid.

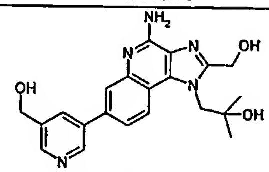
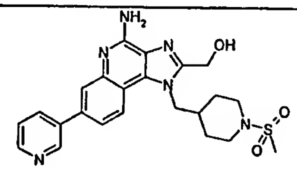
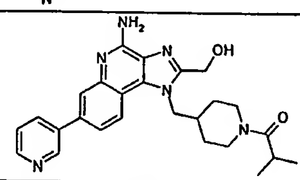
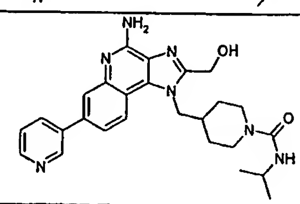
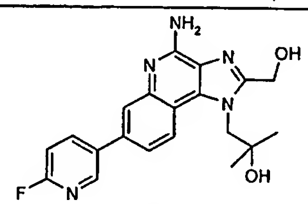
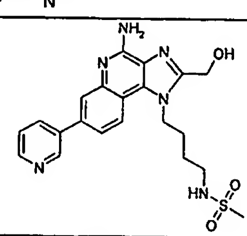
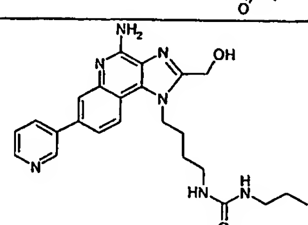
Part F

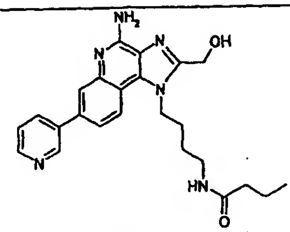
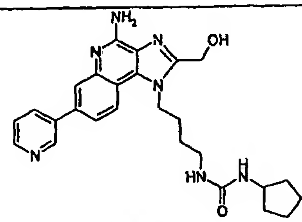
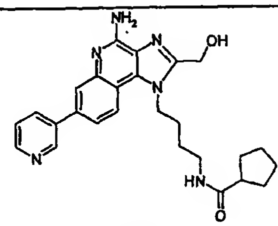
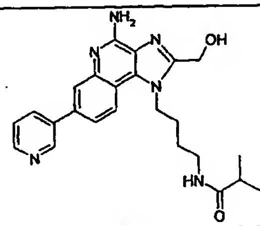
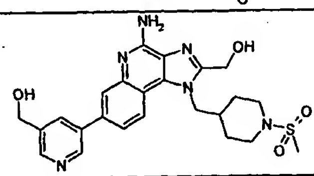
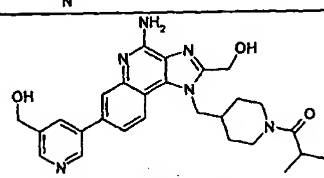
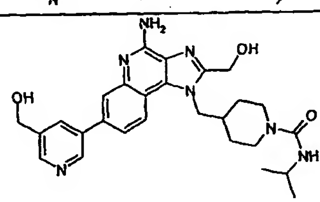
To a mixture of [4-amino-7-bromo-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol (500 mg, 1.28 mmol), 3-pyridyl boronic acid (233 mg, 1.90 mmol), potassium carbonate (579 mg, 4.20 mmol), dimethoxyethane (5 mL), and water (2.5 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_2Cl_2$ (18 mg, 0.026 mmol). The resulting suspension was refluxed for 2 hours. The reaction was cooled to ambient temperature. The reaction mixture was diluted with chloroform and placed directly onto a silica gel column. Chromatography (SiO_2, 0-40% CMA/$CHCl_3$) gave material that was stirred in methanol and filtered to provide 263 mg of [4-amino-7-pyridin-3-yl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as tan crystals, m.p. 260-262 °C. MS (APCI) *m/z* 500.3 $(M + H)^+$; Anal. calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95; N, 17.98. Found: C, 67.49; H, 5.87; N, 17.83.

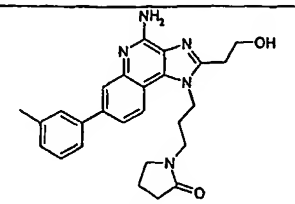
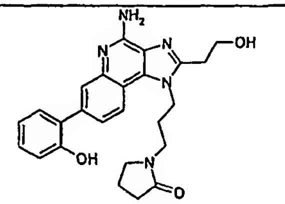
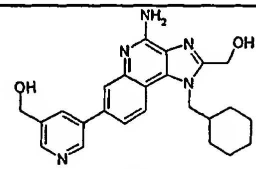
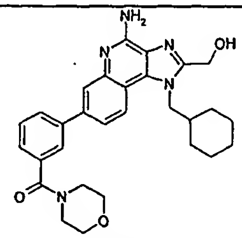
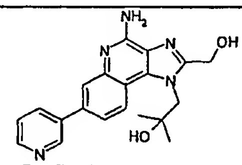
Examples 189 – 207

The compounds in the table below were prepared according to the following general procedure. The ether analog was dissolved or suspended in a solvent such as dichloromethane and the reaction mixture was stirred at 0 °C or at ambient temperature. Boron tribromide (2.5-10 equivalents, 1 M solution in dichloromethane) was added dropwise to the reaction mixture. The reaction was stirred at ambient temperature for 4 h – 6 days after which it was quenched by the careful addition of methanol or water and the solvent was removed under reduced pressure. The product was isolated by a procedure similar to that described below. The residue was combined with 2-6 M hydrochloric acid, heated to 50°C, and stirred for 1-2 hours. The resulting solution was cooled (ice bath) and then free-based (pH 9) with the addition of 2-6 M aqueous sodium hydroxide. The desired material was extracted from the aqueous using an organic solvent such as dichloromethane, ethyl acetate, or chloroform. The organic layer was separated, dried

($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to afford the crude product. The final compound was isolated by prep HPLC (ISCO Combiflash Separation System or Analogix Purification System).

Example	Structure	Analytical Data
189		Off-white needles, mp 180-182 °C. Anal. calcd for $C_{21}H_{23}N_5O_3$•$2.60H_2O$: C, 57.29; H, 6.46; N, 15.91. Found: C, 57.32; H, 6.15; N, 15.73; MS (APCI) *m/z* 394 $(M+H)^+$.
190		Off-white needles, mp 196-198 °C. Anal. calcd for $C_{23}H_{26}N_6O_3S$: C, 59.21; H, 5.62; N, 18.01. Found: C, 59.16; H, 5.84; N, 17.98; MS (APCI) *m/z* 467 $(M+H)^+$.
191		Off-white needles, mp 154-157 °C. Anal. calcd for $C_{26}H_{30}N_6O_2$•$0.25H_2O$: C, 67.44; H, 6.64; N, 18.15. Found: C, 67.48; H, 6.55; N, 18.00; MS (APCI) *m/z* 459 $(M+H)^+$.
192		Off-white needles, mp 182-184 °C. Anal. calcd for $C_{26}H_{31}N_7O_2$: C, 65.94; H, 6.60; N, 20.70. Found: C, 65.70; H, 6.49; N, 20.39); MS (APCI) *m/z* 474 $(M+H)^+$.
193		Beige needles, mp 111-114 °C. Anal. calcd for $C_{20}H_{20}FN_5O_2$•$2.0\ H_2O$: C, 57.55; H, 5.79; N,16.78. Found: C,57.33; H, 5.57; N, 16.76 MS (APCI) *m/z* 382 $(M+H)^+$
194		Off-white solid, mp 188-190 °C Anal. calcd for $C_{21}H_{24}N_6O_3S$•$1.70H_2O$ C: 53.53, H: 5.86, N: 17.84. Found: C: 53.23, %H: 5.62, N: 17.81. MS (APCI) *m/z* 459 $(M+H)^+$
195		Green solid, mp 206-209 °C Anal. calcd for $C_{24}H_{29}N_7O_2$•$0.27H_2O$ C: 63.72, H: 6.58, N: 21.67. Found: C: 63.97, H: 6.26, N: 21.64. MS (APCI) *m/z* 448 $(M+H)^+$

196		Off-white solid, mp 211-212 °C Anal. calcd for $C_{24}H_{28}N_6O_2$•$0.25H_2O$ C: 65.96, H: 6.57, N: 19.23.Found: C: 65.52 H: 6.38, N: 19.38 MS (APCI) *m/z* 433 $(M+H)^+$
197		Yellow solid, mp 225-227 °C Anal. calcd for $C_{26}H_{31}N_7O_2$•$0.38H_2O$ C: 65.00, H: 6.66, N: 20.41. Found: C: 65.26, H: 6.53, N: 20.42. MS (APCI) *m/z* 474 $(M+H)^+$
198		White solid, mp 241-242 °C Anal. calcd for $C_{26}H3_0N_6O_2$ C: 68.10, H: 6.59, N: 18.33. Found: C: 67.85, H: 6.48, N: 18.32. MS (APCI) *m/z* 459 $(M+H)^+$
199		White solid, mp 225-227 °C Anal. calcd for $C_{24}H_{28}N_6O_2$•$0.38H_2O$ C: 65.61, H: 6.60, N: 19.13. Found: C: 65.19, H: 6.74, N: 18.96. MS (APCI) *m/z* 433 $(M+H)^+$
200		White solid, mp >300 °C. Anal. calcd for $C_{24}H_{28}N_6O_4S$•HBr •$0.2H_2O$: C, 49.61; H, 5.10; N, 14.46. Found: C, 49.26; H, 4.84; N, 14.29 MS (APCI) *m/z* 497 $(M+H)^+$
201		Tan solid, mp >300 °C. Anal. calcd for $C_{27}H_{32}N_6O_3$•HBr: C, 56.94; H, 5.84; N, 14.76. Found: C, 56.66; H, 5.69; N, 14.63. MS (APCI) *m/z* 489 $(M+H)^+$
202		Off-white solid, mp >300 °C. Anal. calcd for $C_{27}H_{33}N_7O_3$•HBr: C, 55.14; H, 5.90; N, 16.67. Found: C, 54.86; H, 5.60; N, 16.64. MS (APCI) *m/z* 504 $(M+H)^+$

203		Off white needles, mp 218-221 °C Anal. calcd for $C_{26}H_{29}N_5O_2$•1.25 H_2O: C, 67.00; H, 6.81; N, 15.03. Found: C, 67.04; H, 6.78, N, 14.90. MS (APCI) *m/z* 444 $(M+H)^+$
204		Off white solid, mp >250 °C Anal. calcd for $C_{25}H_{27}N_5O_3$•0.75 H_2O: C, 65.41; H, 6.26; N, 15.26. Found: C, 65.48; H, 6.40; N, 15.07. MS (APCI) *m/z* 446 $(M+H)^+$
205		Off-white solid, mp 166-170 °C Anal. calcd for $C_{24}H_{27}N_5O_2$•0.9 H_2O: C, 66.46; H, 6.69; N, 16.15. Found: C, 66.09; H, 6.73; N, 15.97. MS (APCI) *m/z* 418 $(M + H)^+$
206		Off-white solid, mp 260-264 °C Anal. calcd for $C_{29}H_{33}N_5O_3$•0.6 H_2O•1.0 HCl: C, 63.69; H, 6.49; N, 12.81. Found: C, 63.37; H, 6.23; N, 12.62. MS (APCI) *m/z* 500 $(M + H)^+$
207		Off-white needles, mp 141-143 °C Anal. calcd for $C_{20}H_{21}N_5O_2$•1.00CH_4O• 1.0 H_2O : C, 61.15 H, 6.35 N, 16.98. Found: C, 61.15 H, 6.06 N, 17.34. MS (APCI) *m/z* 364 $(M + H)^+$

Examples 208 – 318

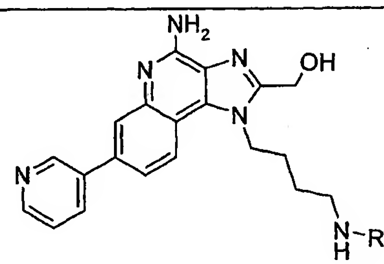
Part A

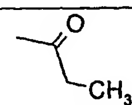
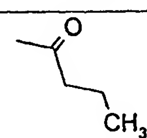
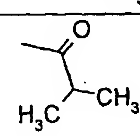
A solution of 1-(4-aminobutyl)-2-ethoxymethyl-7-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline-4-amine (43 mg, 0.10 mmol, 1 eq, U.S. Patent Application Publication 2004/0147543, Example 372) and triethylamine (5 eq) in chloroform (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed overnight and then purified by solid-supported liquid-liquid extraction according to the following procedure. The reaction mixture was loaded onto diatomaceous earth that had been equilibrated with 1 N sodium hydroxide (600 μL) for about 20 minutes. After 10 minutes chloroform (300 μL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated

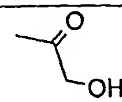
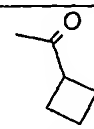
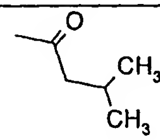
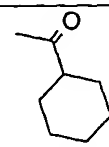
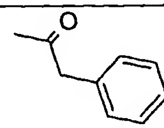
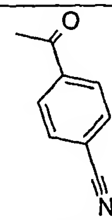
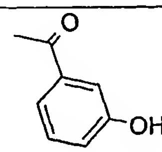
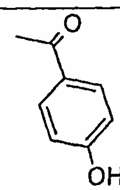
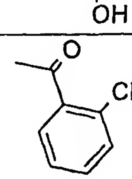
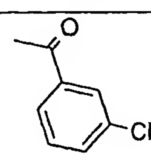
with additional chloroform (500 µL). The solvent was then removed by vacuum centrifugation.

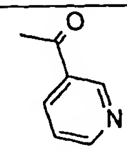
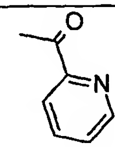
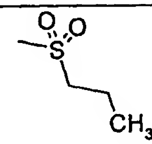
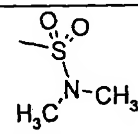
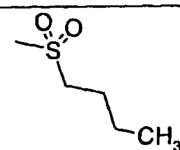
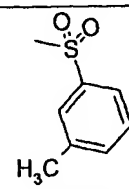
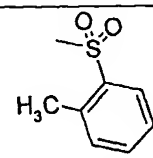
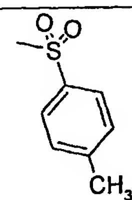
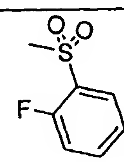
Part B

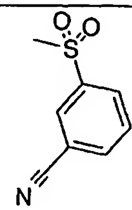
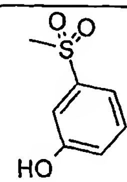
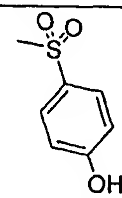
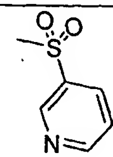
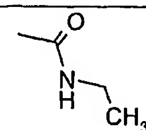
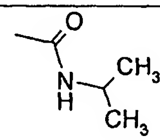
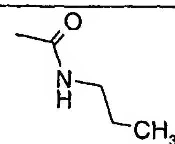
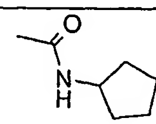
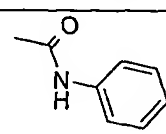
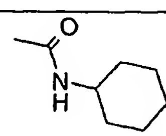
The material from Part A was dissolved in dichloromethane (600 µL) and the solution was cooled to 0 °C. Boron tribromide (400 µL of 1 M in dichloromethane) was added, the reaction mixture was vortexed, chilled for 15 minutes, and then vortexed at ambient temperature overnight. The solvent was removed by vacuum centrifugation. Methanol (300 µL) and 6 N hydrochloric acid (300 µL) were added and the reaction mixture was vortexed for 10 minutes. The solvent was removed by vacuum centrifugation. The compounds were purified as described above for Examples 156 – 161. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

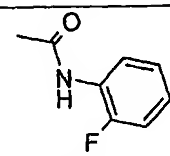
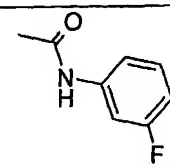
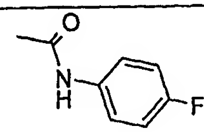
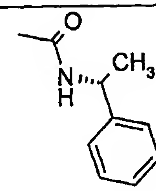
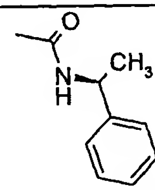
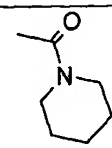
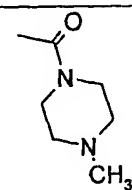


Example	Reagent	R	Measured Mass (M+H)
208	None	—H	363.1964
209	Propionyl chloride		419.2168
210	Cyclopropanecarbonyl chloride		431.2213
211	Butyryl chloride		433.2345
212	Isobutyryl chloride		433.2346

213	Methoxyacetyl chloride		421.1982
214	Cyclobutanecarbonyl chloride		445.2338
215	Isovaleryl chloride		447.2536
216	Cyclohexanecarbonyl chloride		473.2679
217	Phenylacetyl chloride		481.2368
218	4-Cyanobenzoyl chloride		492.2143
219	3-Methoxybenzoyl chloride		483.2121
220	*p*-Anisoyl chloride		483.2115
221	2-Chlorobenzoyl chloride		501.1813
222	3-Chlorobenzoyl chloride		501.1812

223	Nicotinoyl chloride hydrochloride		468.2122
224	Picolinoyl chloride hydrochloride		468.2124
225	1-Propanesulfonyl chloride		469.2039
226	Dimethylsulfamoyl chloride		470.1961
227	1-Butanesulfonyl chloride		483.2160
228	3-Methylbenzenesulfonyl chloride		517.2044
229	*o*-Toluenesulfonyl chloride		517.2071
300	*p*-Toluenesulfonyl chloride		517.2020
301	2-Fluorobenzenesulfonyl chloride		521.1786

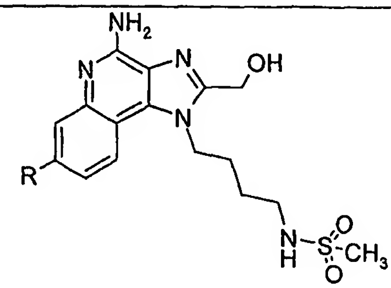
302	3-Cyanobenzenesulfonyl chloride		528.1805
303	3-Methoxybenzenesulfonyl chloride		519.1829
304	4-Methoxybenzenesulfonyl chloride		519.1799
305	3-Pyridinesulfonyl chloride hydrochloride		504.1852
306	Ethyl isocyanate		434.2307
307	Isopropyl isocyanate		448.2498
308	*n*-Propyl isocyanate		448.2448
309	Cyclopentyl isocyanate		474.2629
310	Phenyl isocyanate		482.2338
311	Cyclohexyl isocyanate		488.2759

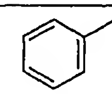
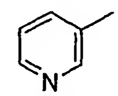
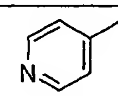
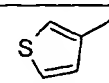
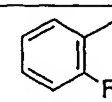
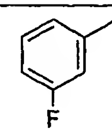
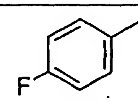
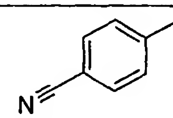
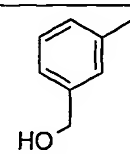
312	2-Fluorophenyl isocyanate		500.2209
313	3-Fluorophenyl isocyanate		500.2206
314	4-Fluorophenyl isocyanate		500.2209
315	(*R*)-(+)-*alpha*-Methylbenzyl isocyanate		510.2580
316	(*S*)-(-)-*alpha*-Methylbenzyl isocyanate		510.2588
317	1-Piperidinecarbonyl chloride		474.2606
318	4-Methyl-1-piperazinecarbonyl chloride		489.2725

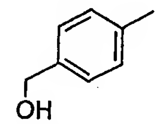
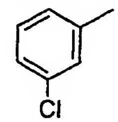
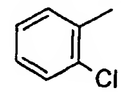
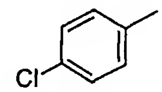
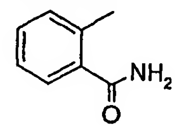
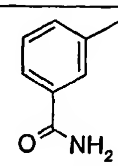
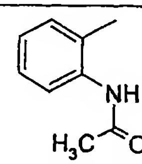
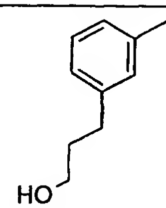
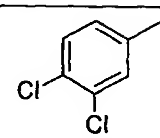
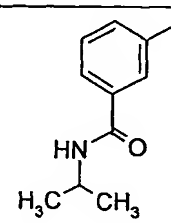
Examples 319 – 345

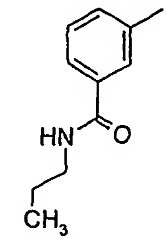
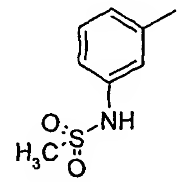
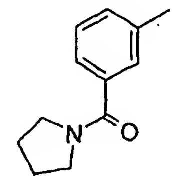
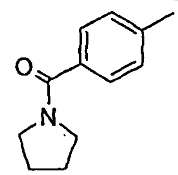
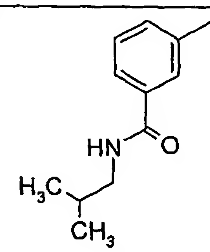
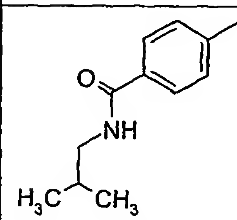
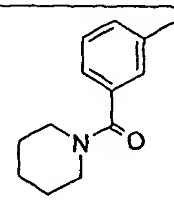
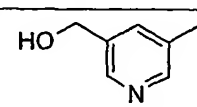
The compounds in the table below were prepared and purified according to the general method of Examples 162 – 186 using *N*-{4-[4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}methanesulfonamide (U.S. Patent Application Publication 2004/0147543, Example 612) in lieu of 1-(4-amino-7-bromo-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol. Prior to purification by solid phase extraction, the reaction mixture for Example 345 was combined with water (500 µL),

glacial acetic acid (500 µL), and tetrahydrofuran (500 µL) and then heated at 60 °C for 2 hours. The table below shows the boronic acid, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



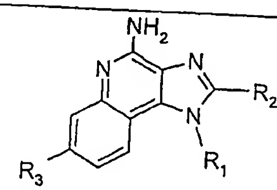
Example	Reagent	R	Measured Mass (M+H)
319	Phenylboronic acid		440.1745
320	Pyridine-3-boronic acid		441.1745
321	Pyridine-4-boronic acid		441.1679
322	Thiophene-3-boronic acid		446.1307
323	2-Fluorophenylboronic acid		458.1668
324	3-Fluorophenylboronic acid		458.1671
325	4-Fluorophenylboronic acid		458.1674
326	4-Cyanophenylboronic acid		465.1684
327	3-(Hydroxymethyl)phenylboronic acid		470.1882

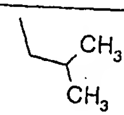
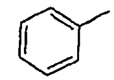
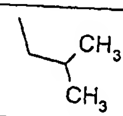
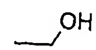
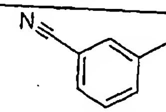
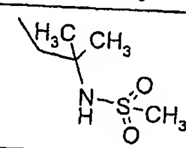
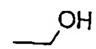
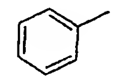
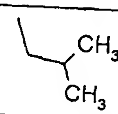
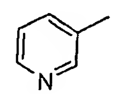
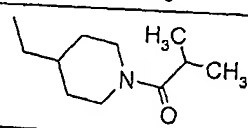
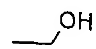
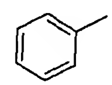
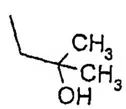
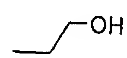
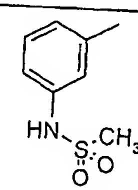
328	4-(Hydroxymethyl)phenylboronic acid		470.1909
329	3-Chlorophenylboronic acid		474.1408
330	2-Chlorophenylboronic acid		474.1366
331	4-Chlorophenylboronic acid		474.1384
332	(2-Aminocarbonylphenyl)boronic acid		483.1796
333	(3-Aminocarbonylphenyl)boronic acid		483.1812
334	(2-Acetylaminophenyl)boronic acid		497.1938
335	[3-(3-Hydroxypropyl)phenyl]boronic acid		498.2136
336	3,4-Dichlorophenylboronic acid		508.0989
337	3-(*N*-Isopropylaminocarbonyl)phenylboronic acid		525.2331

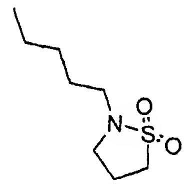
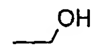
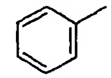
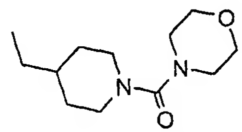
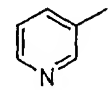
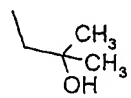
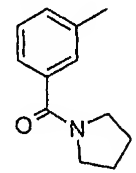
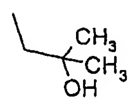
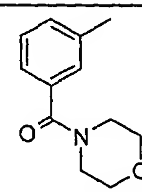
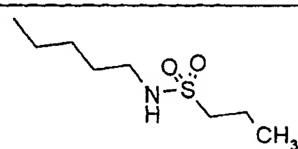
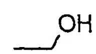
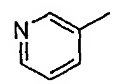
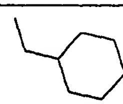
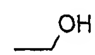
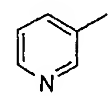
338	3-(*N*-Propylaminocarbonyl)phenylboronic acid		525.2284
339	3-(Methylsulfonylamino)phenylboronic acid		533.1659
340	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		537.2320
341	4-(Pyrrolidine-1-carbonyl)phenylboronic acid		537.2271
342	3-(Isobutylaminocarbonyl)phenylboronic acid		539.2418
343	4-(Isobutylaminocarbonyl)phenylboronic acid		539.2429
344	3-(Piperidine-1-carbonyl)phenylboronic acid		551.2483
345	5-*tert*-butyldimethylsilanyloxy-methyl)pyridine-3-boronic acid		471.1819

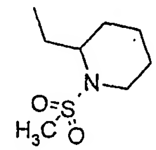
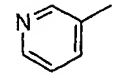
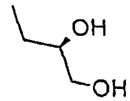
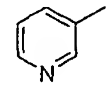
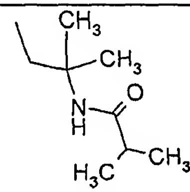
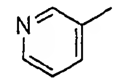
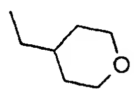
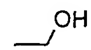
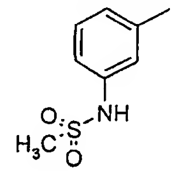
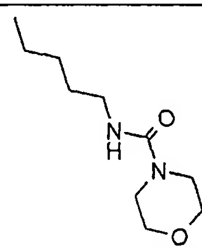
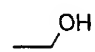
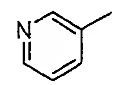
Examples 346 – 362

The compounds in the table below were prepared according to the following method. A test tube containing a solution of the corresponding ether analog (ethoxymethyl or methoxyethyl) in dichloromethane (1 mL) was cooled to 0 °C in an ice bath. Boron tribromide (4 eq of 1 M in dichloromethane) was added. The tube was vortexed, maintained at 0 °C for 0.5 hr, and then stirred at ambient temperature for 9 hours. Methanol (1 mL) and 6 N hydrochloric acid (500 µL) were added and the tube was vortexed for 5 minutes. The solvent was removed by vacuum centrifugation. The compounds were purified as described above for Examples 156-161. The table below shows a reference for the starting ether, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reference for ether starting material	R_1	R_2	R_3	Measured Mass (M+H)
346	Example 102				347.1904
347	Example 111				372.1819
348	Example 201				440.1755
349	Example 113				348.1810
350	Example 194				458.2540
351	Example 139				470.1832

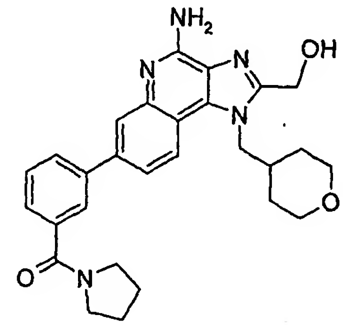
352	Example 152				466.1897
353	Example 180				502.2554
354	Example 129				460.2326
355	Example 130				476.2285
356	Example 376				469.2024
357	Example 438				388.2130

358	Example 492				467.1852
359	Example 488				366.1574
360	Example 422				433.2374
361	Example 480				482.1815
362	*				476.2383

*Although not specifically exemplified, the compound is readily prepared using the disclosed synthetic methods.
All references are to U.S. Patent Application Publication 2004/0147543.

Example 363

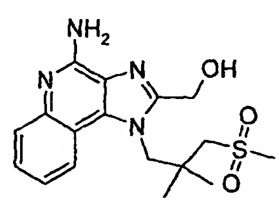
[4-Amino-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol



To a mixture of [4-amino-7-bromo-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-imidazo[4,5-c]quinolin-2-yl]methanol (400 mg, 1.00 mmol), 3-pyrrolidinylcarbonyl phenyl boronic acid (328 mg, 1.50 mmol), potassium carbonate (455 mg, 3.30 mmol), dimethoxyethane (4 mL), and water (2 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol). The resulting suspension was refluxed for 18 hours. The reaction was cooled to ambient temperature. The reaction mixture was diluted with water and extracted with chloroform. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 0-40% CMA/$CHCl_3$) gave material that was stirred in acetonitrile and filtered to provide 100 mg of [4-amino-7-[3-(pyrrolidin-1-ylcarbonyl)phenyl]-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as a white powder, m.p. 281-284 °C. MS (APCI) *m/z* 486.3 $(M + H)^+$; Anal. calcd for $C_{28}H_{31}N_5O_3$: C, 69.26; H, 6.43; N, 14.42. Found: C, 68.99; H, 6.16; N, 14.46.

Example 364

{4-Amino-1-[2,2-dimethyl-3-(methylsulfonyl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}methanol

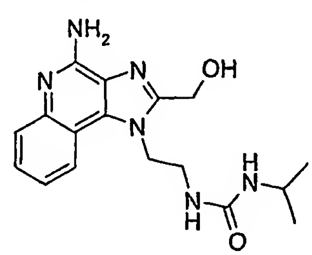


To a suspension of 1-[2,2-dimethyl-3-(methylsulfonyl)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.4 g, 1.02 mmol) in dichloromethane (5 mL) was added boron tribromide (5.1 mL, 1M solution in dichloromethane). An exotherm was observed upon addition and the mixture turned light purple. After stirring at ambient temperature for 20 hours, the remaining starting material was consumed by adding boron tribromide (2.5 mL, 1M solution in dichloromethane). The reaction was quenched with aqueous hydrochloric acid (1N, 20 mL) to afford a homogeneous mixture. The layers were separated and the aqueous layer washed with dichloromethane (20 mL). The pH of the aqueous layer was adjusted to 12 by addition of aqueous sodium hydroxide (50%) at which time a solid precipitated out of solution. The solid was stirred for 18 hours, collected by filtration and washed with water. The crude product was purified by chromatography over silica gel (eluting with CMA) to afford a white powder. The powder was triturated with methanol (20 mL). The resulting solid was isolated by filtration, washed with methanol and dried for 4 hours at 65 °C to provide 150 mg of {4-amino-1-[2,2-dimethyl-3-(methylsulfonyl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-2-yl}methanol as a white powder, mp 230-232 °C.

Anal. Calcd for $C_{17}H_{22}N_4O_3S$: %C, 56.33; %H, 6.12; %N, 15.46. Found: %C, 56.33; %H, 6.31; %N, 15.27.

Example 365

N-{2-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N*'-isopropylurea



A stirring solution of *N*-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N*'-isopropylurea (400 mg, 1.1 mmol) in dichloromethane (50 mL) was sealed with a septum and purged with nitrogen gas. The solution was cooled in an ice/water bath and a 1.0 M solution of boron tribromide in dichloromethane (2.2 mL) was

added via syringe. The resulting mixture was stirred for 2 hours while warming to ambient temperature. The mixture was cooled back to 0 °C in an ice/water bath and the second portion of boron tribromide (1.0 M, 5.5 mL) was added. The reaction was stirred for 18 hours while warming to ambient temperature. Aqueous hydrochloric acid (6N, 10 ml) was added and the mixture was stirred for 1 hour. The layers were separated and the aqueous fraction was neutralized by the slow addition of solid sodium hydroxide until the pH reached 14. A fine precipitate formed. The aqueous mixture was extracted with chloroform (2x 50 mL) and filtered. The resulting solid (filter cake) was combined with the organic extracts, methanol (50 mL), and silica gel (5 g). The mixture was concentrated under reduced pressure. The crude product absorbed on silica was purified by chromatography using a HORIZON HPFC system (silica cartridge, eluting with 0-35% CMA in chloroform over 2.6 L) followed by recrystallization from acetonitrile to provide 170 mg of *N*-{2-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N*'-isopropylurea as an off-white solid, mp >240 °C.

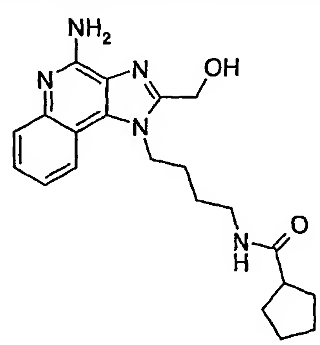
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 7.9 Hz, 1H), 7.61 (dd, J = 8.3, 0.9 Hz, 1H), 7.43 (m, 1H), 7.24 (m, 1H), 6.53 (br s, 2H), 5.99 (t, J = 5.8 Hz, 1H), 5.82 (d, J = 7.8 Hz, 1H), 5.67 (d, J = 5.8 Hz, 1H), 4.75 (d, J = 5.8 Hz, 2H), 4.66 (t, J = 6.7 Hz, 2H), 3.69 (m, 1H), 3.48 (q, J = 6.4 Hz, 2H), 1.01 (d, J = 6.5 Hz, 6H);

MS (APCI) m/z 343 $(M + H)^+$;

Anal. Calcd. for $C_{17}H_{22}N_6O_2$: %C, 59.63; %H, 6.48; %N, 24.54. Found: %C, 59.64; %H, 6.59; %N, 24.58.

Example 366

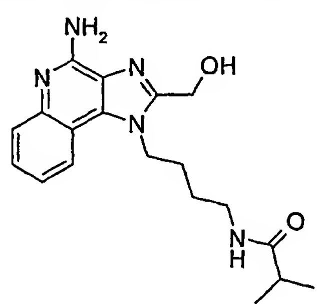
N-{4-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide



Boron tribromide (2.5 equivalents, 14.6 mL of 1 M solution in dichloromethane) was added dropwise to a cooled (ice bath) suspension of *N*-{4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide (2.4 g, 5.8 mmol) in dichloromethane (25 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred for 6 days. Additional boron tribromide (5 equivalents, 29 mmol, 29 mL) was added and the reaction was stirred at ambient until starting material was consumed. The reaction was quenched slowly with methanol (100 mL) and then concentrated under reduced pressure. The residue was combined with 6 M hydrochloric acid (100 mL), heated to 50°C, and stirred for 2 hours. The resulting solution was cooled (ice bath) and then free-based (pH 9) with the addition of 6 M aqueous sodium hydroxide. A brown gummy solid formed in the basic aqueous solution. The aqueous liquid was decanted from the solid and acetonitrile was added (30 mL). A white precipitate formed and was isolated by filtration. The white precipitate was then triturated with hot acetonitrile, allowed to cool, isolated by filtration, washed with ether, and dried under vacuum to provide *N*-{4-[4-amino-2-(hydroxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}cyclopentanecarboxamide (0.48 g) as a fine white solid, mp 183-186°C; MS (ESI) *m/z* 382 $(M+H)^+$; Anal. Calcd for $C_{21}H_{27}N_5O_2$: C, 65.35; H, 7.18; N, 18.14; Found C, 65.06; H, 6.90; N, 18.13.

Example 367

N-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]isobutyramide

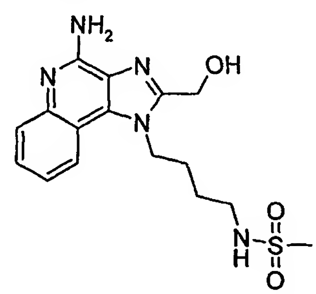


Boron tribromide (2.5 equivalents, 15.6 mL of 1 M solution in dichloromethane) was added dropwise to a cooled (ice bath) suspension of *N*-[4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-c]quinolin-1-yl)butyl]isobutyramide (2.4 g, 6.2 mmol) in dichloromethane (25 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred for 1 day. Additional boron tribromide (5 equivalents, 31

mmol, 31 mL) was added to the mixture. The reaction was quenched slowly with methanol (100 mL) and then concentrated under reduced pressure. The residue was combined with 6 M hydrochloric acid (100 mL), heated to 50°C, and stirred for 2 hours. The resulting solution was cooled (ice bath) and then free-based (pH 9) with the addition of 6 M sodium hydroxide. A brown gummy solid formed in the basic aqueous solution. The resulting solid was extracted with dichloromethane (6 x 50 mL). The combined extracts were washed with brine (100 mL), dried with magnesium sulfate, filtered, and then concentrated under reduced pressure. This material was purified by prep HPLC (Analogix Separation System, Biotage Si 40+M column, eluted with a gradient of 0-20% methanol in dichloromethane with 1% ammonium hydroxide) to provide a light brown solid. The solid was triturated with hot acetonitrile, allowed to cool, isolated by filtration, washed with ether, and dried under vacuum to provide *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]isobutyramide (0.049 g) as a white solid, mp 222-224°C; MS (ESI) *m/z* 356 $(M+H)^+$; Anal. Calcd for $C_{19}H_{25}N_5O_2 \cdot 0.25HBr \cdot 0.10H_2O$: C, 60.46; H, 6.80; N, 18.55; Found C, 60.26; H, 6.64; N, 18.43.

Example 368

N-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide

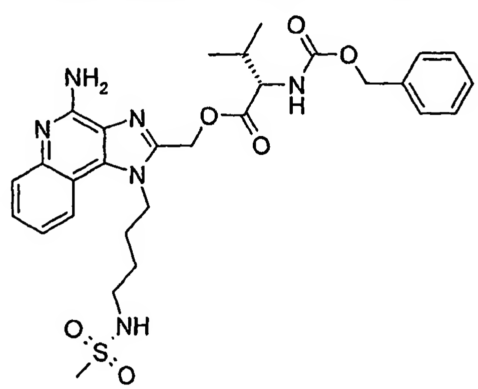


Boron tribromide (2.5 equivalents, 20 mL of 1 M solution in dichloromethane) was added dropwise to a cooled (ice bath) suspension of *N*-[4-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (3g, 7.92 mmol) in dichloromethane (20 mL). The reaction mixture was allowed to slowly warm to ambient temperature and then stirred for 4 hours. Additional boron tribromide (2 mL) was added and the mixture was stirred for 3 hours. The reaction was quenched slowly with methanol (20 mL) and then concentrated under reduced pressure. The residue was combined with 6

M hydrochloric acid (50mL), heated to 50°C, and stirred for 2 hours. The resulting solution was concentrated under reduced pressure to a slurry that cooled (ice bath) and then free-based with the addition of 7 M ammonia in methanol (40 mL). The mixture was concentrated under reduced pressure and the addition of 7 M ammonia in methanol (40mL) was repeated 2 more times. The concentrated brown sludge like material was purified by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of methanol in dichloromethane with 1% ammonium hydroxide) to provide a light brown solid. The solid was triturated with hot acetonitrile, allowed to cool, isolated by filtration, washed with ether, and dried under vacuum to provide *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (0.1 g) as a fine beige solid, mp 216-219°C; MS (ESI) *m/z* 364 $(M+H)^+$; Anal. Calcd for $C_{16}H_{21}N_5O3S$: C, 52.88; H, 5.82; N, 19.27; Found C, 52.62; H, 5.71; N, 19.02.

Example 369

(4-Amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl *N*-[(benzyloxy)carbonyl]-L-valinate

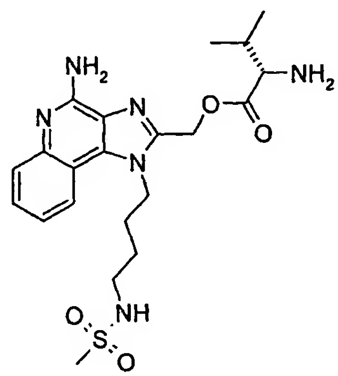


To a stirred suspension of *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide (2.1 g, 5.8 mmol) in THF was added triphenylphosphine (1.5 equivalents, 8.7 mmol, 2.2 g) followed by CBZ-L-valine (1.5 equivalents, 8.7 mmol, 2.3 g). The suspension was stirred for 5 min after which it was cooled in an ice-bath. To this cooled reaction mixture diisopropyl azodicarboxylate (DIAD,1.8 equivalents, 10.4 mmol, 2.0 mL) was added and the reaction was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the crude solid was purified by prep HPLC (ISCO Combiflash Separation

System, Biotage Si 40+M column, eluted with a gradient of 0-8% methanol in dichloromethane with 1% ammonium hydroxide) to provide a solid. The solid was heated in diethyl ether and filtered to afford (4-amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl *N*-[(benzyloxy)carbonyl]-L-valinate (2 g) as a beige solid, mp 99-100°C; MS (ESI) *m/z* 597 $(M+H)^+$; Anal. Calcd for $C_{29}H_{36}N_6O_6S$: C, 58.37; H, 6.08; N, 14.08; Found C, 57.98; H, 6.31; N, 13.82.

Example 370

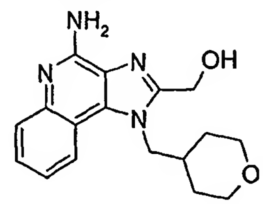
(4-Amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl L-valinate



To a hydrogenation bottle was added (4-amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl *N*-[(benzyloxy)carbonyl]-L-valinate (1.5 g, 2.5 mmol) followed by a mixture of methanol (30 mL), THF (15 mL) and water (5 mL) and conc HCl (5 mL). To this was added Pd/C (90 mg) and the reaction was hydrogenated at 40 psi (2.8 X 10^5 Pa) overnight. To the reaction mixture was added conc. HCl (5 mL) and Pd/C (90 mg) and the reaction was hydrogenated at 40 psi (2.8 X 10^5 Pa) for 18 hours. The reaction was filtered through CELITE filter aid and the filtrate was evaporated to afford a clear oil. The product was isolated by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of 0-8% methanol in dichloromethane with 1% ammonium hydroxide) to provide (4-amino-1-{4-[(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl L-valinate (0.495 g) as an off white solid, mp 161-163°C; MS (ESI) *m/z* 463 $(M+H)^+$; Anal. Calcd for $C_{21}H_{30}N_6O_4S$: C, 54.53; H, 6.54; N, 18.17; Found C, 53.96; H, 6.62; N, 17.85, delta C = 0.57.

Example 371

[4-Amino-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol



Part A

Under a nitrogen atmosphere THF (90 mL) and triethylamine (17.5 mL, 125.6 mmol) were added sequentially to a mixture of crude 4-chloro-3-nitroquinoline (13.10 g, 62.81 mmol) and 1-tetrahydro-2*H*-pyran-4-ylmethylamine hydrochloride (10.0 g, 65.95 mmol). The reaction mixture was placed in an oil bath at 45 °C for 1 hour and then concentrated under reduced pressure. The residue was diluted with THF (30 mL) and water (200 mL). The THF was removed under reduced pressure. A solid was isolated by filtration and dried to provide 16.10 g of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine as a light yellow solid.

Part B

A mixture of 3-nitro-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)quinolin-4-amine (2.50 g), 10% palladium on carbon (0.25 g), and ethanol (40 mL) was placed under hydrogen pressure on a Parr apparatus. When the reaction was complete, the mixture was filtered through a layer of CELITE filter agent. The filter cake was washed with ethanol. The filtrate was concentrated under reduced pressure to provide 2.23 g of N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine as a yellowish-orange oil.

Part C

Chloroacetyl chloride (12 mL, 151 mmol) was dissolved in dichloromethane (30 mL) and added via addition funnel, over 20 minutes, to a stirring solution of N^4-(tetrahydro-2*H*-pyran-4-ylmethyl)quinoline-3,4-diamine (35.3g, 137 mmol) in dichloromethane (300 mL). The resulting solution was stirred at ambient temperature under nitrogen for 24 hours at which point the solution was heated to 40 °C for an additional 24 hours. The mixture was cooled to ambient temperature, diluted with dichloromethane (150 mL) and transferred to a separatory funnel. The organic layer was washed with water (2 x 200 mL) and brine (2 x 200 mL), dried over magnesium sulfate,

filtered and concentrated under reduced pressure to provide 38.3 g of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline as a light brown solid.

Part D

3-Chloroperoxybenzoic acid (mCPBA) (3.8 g of 77% pure material, 14.2 mmol) was added to a stirring solution of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinoline (3.0g, 9.50 mmol) in dichloromethane (60 mL). After 15.5 hours, ammonium hydroxide (12 mL) and then *p*-toluenesulfonyl chloride (2.2g, 11.4 mmol) were added to the stirring solution and the biphasic mixture was stirred at ambient temperature for 3 hours. The reaction was diluted with water (50 mL) and then transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (3 x 100 mL) and the combined organic fractions dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using a HORIZON HPFC system (silica cartridge, eluting with 3 – 20% methanol in dichloromethane) to provide 1.6 g of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow solid.

Part E

Potassium acetate (0.41 g, 4.16 mmol) and potassium iodide (0.28g, 1.66 mmol) were added to a stirring solution of 2-(chloromethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.55 g, 1.66 mmol) and the resulting suspension was heated to 50 °C. After 17 hours, the suspension was cooled to ambient temperature and concentrated under reduced pressure. The residue was suspended in methanol (10 mL) and water (5 mL) and lithium hydroxide monohydrate (0.35 g, 8.31 mmol) was added in one portion. The resulting solution was stirred at ambient temperature 18 hours and concentrated under reduced pressure. The residue was diluted with water (20 mL) and neutralized with hydrochloric acid (6 N in water). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and ethyl acetate (50 mL). The combined organic fractions were concentrated to a yellow solid which was crystallized from acetonitrile. The crystals were isolated by filtration and dried in a vacuum oven at 65 °C to provide 0.20 g of [4-amino-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as an off-white solid, mp 239-241 °C.

Anal. calcd for $C_{17}H_{20}N_4O_2 \cdot 0.2H_2O$: C, 64.62; H, 6.51; N, 17.73. Found: C, 64.45; H, 6.69; N, 17.62.

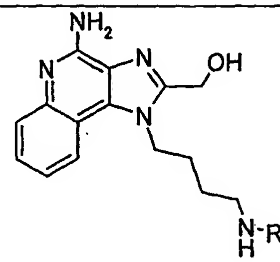
Examples 372 – 450

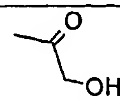
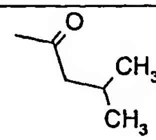
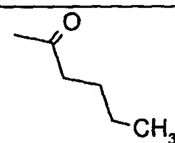
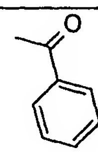
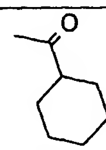
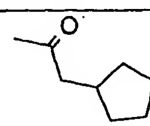
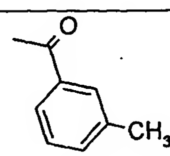
Part A

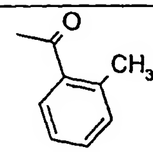
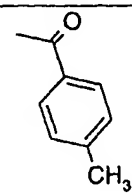
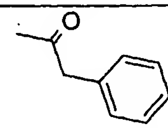
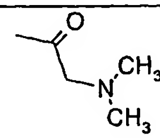
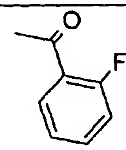
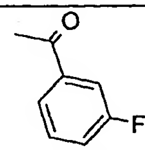
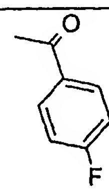
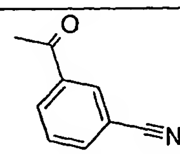
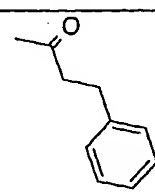
A solution of 1-(4-aminobutyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-4-amine (30 mg, 1 eq, prepared according to the general method of Example 3 using methoxyacetyl chloride in lieu of 3-methoxypropionyl chloride) and *N,N*-diisopropylethylamine (2 eq) in *N,N*-dimethylacetamide (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed overnight and then quenched with water (100 μL). The solvents were removed by vacuum centrifugation. The residue was purified by solid-supported liquid-liquid extraction according to the following procedure. The sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with 1 M sodium hydroxide (600 μL) for about 20 minutes. After 10 minutes chloroform (500 μL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

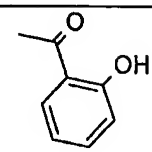
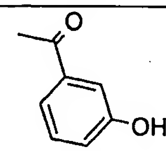
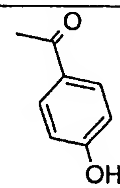
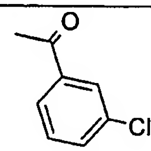
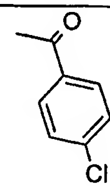
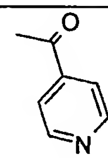
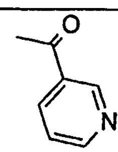
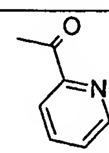
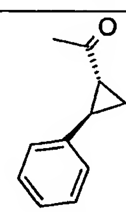
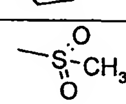
Part B

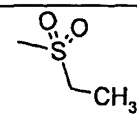
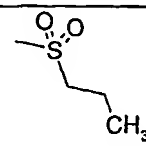
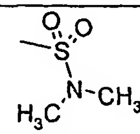
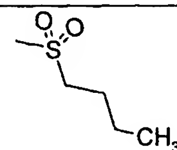
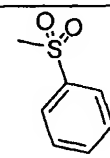
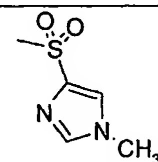
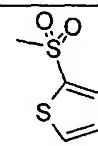
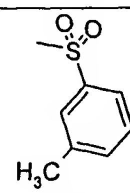
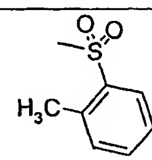
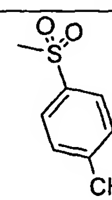
The residue (in a test tube) was combined with dichloromethane (500 μL) and the tube was vortexed to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 μL of 1 M in dichloromethane). The mixture was vortexed for 5 minutes, chilled for 30 minutes, and then vortexed at ambient temperature for 64 hours. Additional dichloromethane (500 μL) and boron tribromide (400 μL of 1 M in dichloromethane) were added and the mixture was vortexed overnight. The solvent was then removed by vacuum centrifugation. The residue was diluted with methanol (500 μL) and hydrochloric acid (500 μL of 6 N). The solvents were removed by vacuum centrifugation. The compounds were purified according to the method described in Examples 8 – 72. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

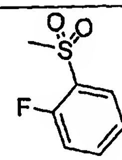
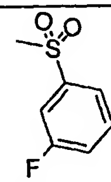
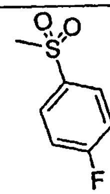
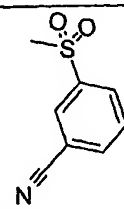
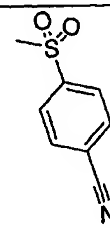
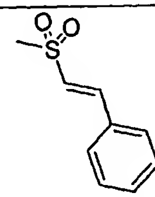
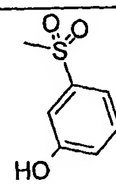
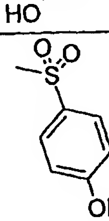


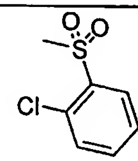
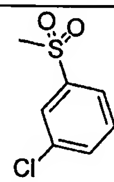
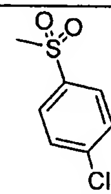
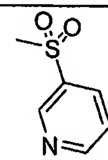
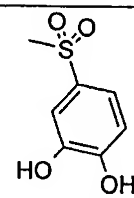
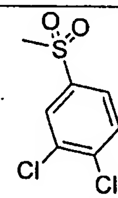
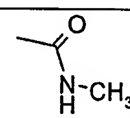
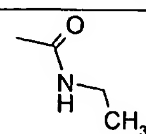
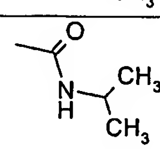
Example	Reagent	R	Measured Mass (M+H)
372	None	H	286.1658
373	Cyclopropanecarbonyl chloride		354.1907
374	Methoxyacetyl chloride		344.1699
375	Cyclobutanecarbonyl chloride		368.2050
376	Isovaleryl chloride		370.2206
377	Pentanoyl chloride		370.2208
378	Benzoyl chloride		390.1909
379	Cyclohexanecarbonyl chloride		396.2412
380	Cyclopentylacetyl chloride		396.2411
381	*m*-Toluoyl chloride		404.2069

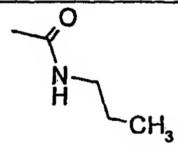
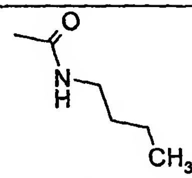
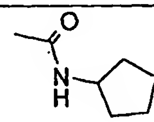
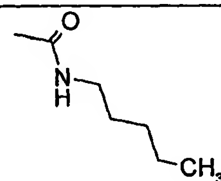
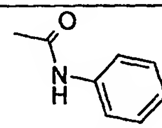
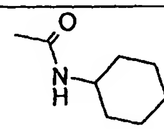
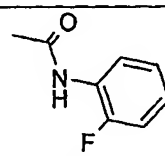
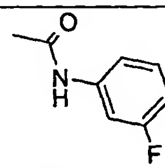
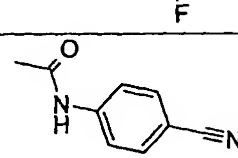
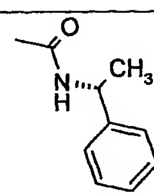
382	*o*- Toluoyl chloride		404.2072
383	*p*- Toluoyl chloride		404.2108
384	Phenylacetyl chloride		404.2056
385	Dimethylaminoacetyl chloride hydrochloride		371.2157
386	2-Fluorobenzoyl chloride		408.1819
387	3-Fluorobenzoyl chloride		408.1811
388	4-Fluorobenzoyl chloride		408.1819
389	3-Cyanobenzoyl chloride		415.1847
390	Hydrocinnamoyl chloride		418.2200

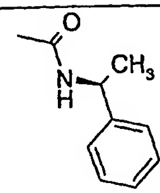
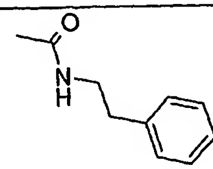
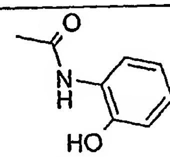
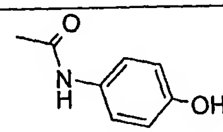
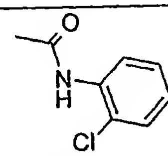
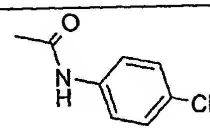
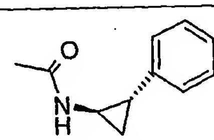
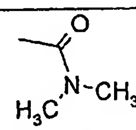
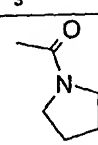
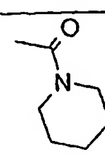
391	2-Methoxybenzoyl chloride		406.1880
392	3-Methoxybenzoyl chloride		406.1876
293	*p*-Anisoyl chloride		406.1860
394	3-Chlorobenzoyl chloride		424.1517
395	4-Chlorobenzoyl chloride		424.1525
396	Isonicotinoyl chloride hydrochloride		391.1874
397	Nicotinoyl chloride hydrochloride		391.1895
398	Picolinoyl chloride hydrochloride		391.1846
399	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		430.2213
400	Methanesulfonyl chloride		364.1421

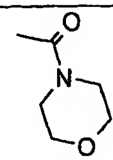
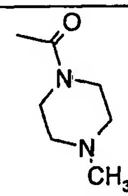
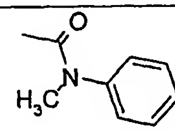
401	Ethanesulfonyl chloride		378.1595
402	1-Propanesulfonyl chloride		392.1753
403	Dimethylsulfamoyl chloride		393.1685
404	1-Butanesulfonyl chloride		406.1881
405	Benzenesulfonyl chloride		426.1591
406	1-Methylimidazole-4-sulfonyl chloride		430.1668
407	2-Thiophenesulfonyl chloride		432.1135
408	3-Methylbenzenesulfonyl chloride		440.1728
409	*o*-Toluenesulfonyl chloride		440.1758
410	*p*-Toluenesulfonyl chloride		440.1766

411	2-Fluorobenzenesulfonyl chloride		444.1479
412	3-Fluorobenzenesulfonyl chloride		444.1517
413	4-Fluorobenzenesulfonyl chloride		444.1496
414	3-Cyanobenzenesulfonyl chloride		451.1568
415	4-Cyanobenzenesulfonyl chloride		451.1579
416	*beta*-Styrenesulfonyl chloride		452.1725
417	3-Methoxybenzenesulfonyl chloride		442.1534
418	4-Methoxybenzenesulfonyl chloride		442.1557

419	2-Chlorobenzenesulfonyl chloride		460.1173
420	3-Chlorobenzenesulfonyl chloride		460.1242
421	4-Chlorobenzenesulfonyl chloride		460.1191
422	3-Pyridinesulfonyl chloride hydrochloride		427.1530
423	3,4-Dimethoxybenzenesulfonyl chloride		458.1452
424	3,4-Dichlorobenzenesulfonyl chloride		494.0806
425	Methyl isocyanate		343.1862
426	Ethyl isocyanate		357.2018
427	Isopropyl isocyanate		371.2181

428	*n*-Propyl isocyanate		371.2187
429	*n*-Butyl isocyanate		385.2314
430	Cyclopentyl isocyanate		397.2312
431	Pentyl isocyanate		399.2512
432	Phenyl isocyanate		405.2047
433	Cyclohexyl isocyanate		411.2473
434	2-Fluorophenyl isocyanate		423.1959
435	3-Fluorophenyl isocyanate		423.1924
436	4-Cyanophenyl isocyanate		430.1979
437	(*R*)-(+)-*alpha*-Methylbenzyl isocyanate		433.2370

438	(*S*)-(-)- *alpha*-Methylbenzyl isocyanate		433.2327
439	2-Phenylethylisocyanate		433.2333
440	2-Methoxyphenyl isocyanate		421.2006
441	4-Methoxyphenyl isocyanate		421.1958
442	2-Chlorophenyl isocyanate		439.1650
443	4-Chlorophenyl isocyanate		439.1656
444	*trans*-2-Phenylcyclopropyl isocyanate		445.2328
445	*N,N*-Dimethylcarbamoyl chloride		357.2005
446	1-Pyrrolidinecarbonyl chloride		383.2168
447	1-Piperidinecarbonyl chloride		397.2329

448	4-Morpholinylcarbonyl chloride		399.2112
449	4-Methyl-1-Piperazinecarbonyl chloride		412.2439
450	*N*-Methyl-*N*-phenylcarbamoyl chloride		419.2167

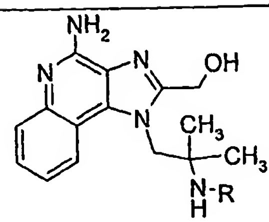
Examples 451 – 466

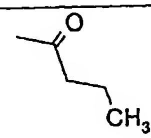
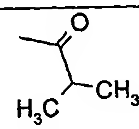
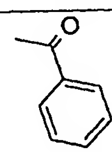
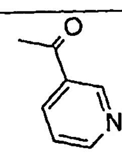
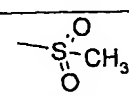
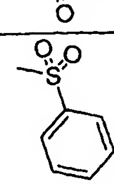
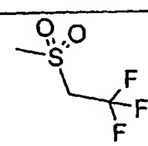
Part A

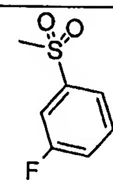
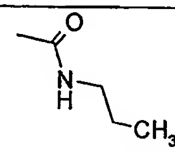
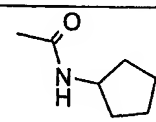
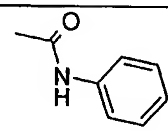
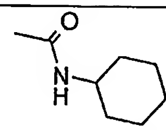
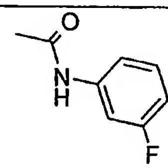
A solution of 1-(2-amino-2-methylpropyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinoline-4-amine (31 mg, 1 eq, prepared according to the general method of Example 3 using methoxyacetyl chloride in lieu of 3-methoxypropionyl chloride and *tert*-butyl *N*-{2-[(3-aminoquinolin-4-yl)amino]-1,1-dimethylethyl}carbamate in lieu of *tert*-butyl *N*-{4-[(3-aminoquinolin-4-yl)amino]butyl}carbamate) and *N,N*-diisopropylethylamine (2 eq) in *N,N*-dimethylacetamide (1 mL) was placed in a test tube. A reagent (1.1 eq) from the table below was added and the reaction mixture was vortexed overnight. The reaction was quenched with concentrated ammonium hydroxide (100 µL) and the solvents were removed by vacuum centrifugation.

Part B

The residue (in a test tube) was combined with dichloromethane (1 mL) and the tube was vortexed to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 µL of 1 M in dichloromethane). The reaction was maintained at about 0 °C for 20 minutes. Methanol (1 mL) and hydrochloric acid (500 µL of 6 N) were added and the tube was vortexed for about 30 minutes. The solvents were removed by vacuum centrifugation. The compounds were purified according to the method described in Examples 8 – 72. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
451	None	—H	286.1687
452	Cyclopropanecarbonyl chloride		354.1936
453	Butyryl chloride		356.2094
454	Isobutyryl chloride		356.2119
455	Cyclopentanecarbonyl chloride		382.2259
456	Benzoyl chloride		390.1908
457	Nicotinoyl chloride hydrochloride		391.1844
458	Methanesulfonyl chloride		364.1414
459	Benzenesulfonyl chloride		426.1617
460	2,2,2-Trifluoroethanesulfonyl chloride		432.1339

461	3-Fluorobenzenesulfonyl chloride		444.1523
462	*n*-Propyl isocyanate		371.2215
463	Cyclopentyl isocyanate		397.2327
464	Phenyl isocyanate		405.2063
465	Cyclohexyl isocyanate		411.2515
466	3-Fluorophenyl isocyanate		423.1955

Examples 467 – 478

Part A

To a round-bottomed flask containing 1-(4-aminobutyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (10.0 g, 33.4 mmol) was added methanol (160 mL) followed by acetic acid (40 mL). The reaction was stirred for 5 minutes and pyridine 3-carboxaldehyde (5.4 g, 50.1 mmol) was added and the reaction was stirred overnight at ambient temperature. Sodium cyanoborohydride (1 M in THF, 33.4 mL, 33.4 mmol) was added to the resultant imine in portions over 10 minutes. After 45 minutes the solvent was evaporated to afford an oil. To the oil was added saturated aqueous sodium bicarbonate (200 mL) and the aqueous layer was washed with ethyl acetate (200 mL) and dichloromethane (200 mL). The product was extracted from the aqueous with 20% methanol (2 x 100 mL) in dichloromethane. The organic layers were combined and the solvent evaporated to afford crude 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (about 2 g). The aqueous

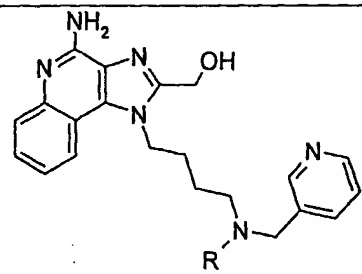
layer was again extracted with 20% dimethylformamide (2 x 100 mL) in dichloromethane. The organic layers were combined and the solvent evaporated to afford crude 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (about 2 g).

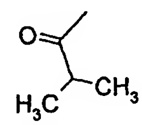
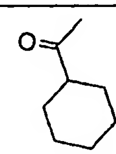
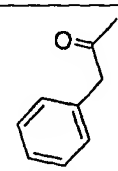
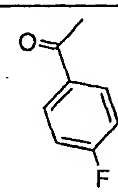
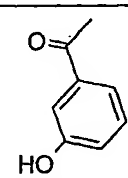
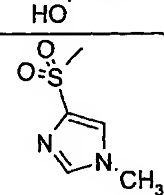
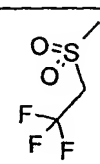
Part B

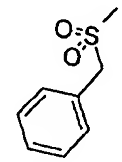
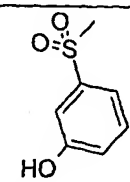
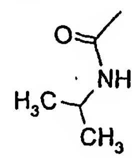
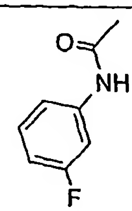
A solution of 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (40 mg, 1 eq) and *N,N*-diisopropylethylamine (2 eq) in *N,N*-dimethylacetamide (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed for 4 hours and then quenched with water (50 µL). The solvents were removed by vacuum centrifugation. The residue was purified by solid-supported liquid-liquid extraction according to the following procedure. The sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with 1 M sodium hydroxide (600 µL) for about 20 minutes. After 10 minutes chloroform (500 µL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 µL). The solvent was then removed by vacuum centrifugation.

Part C

The residue (in a test tube) was combined with dichloromethane (500 µL) and the tube was vortexed to dissolve the solids. The solution was cooled (0 °C) and then combined with boron tribromide (400 µL of 1 M in dichloromethane). The mixture was vortexed for 10 minutes, chilled for 30 minutes, and then vortexed at ambient temperature overnight. The solvent was then removed by vacuum centrifugation. The residue was diluted with methanol (500 µL) and hydrochloric acid (500 µL of 6 N) and the mixture was vortexed for about 30 minutes. The solvents were removed by vacuum centrifugation. The compounds were purified according to the method described in Examples 8 – 72. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

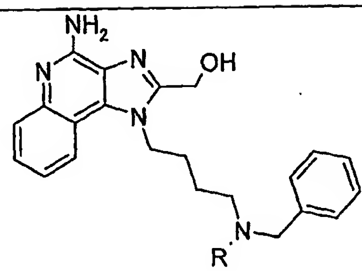


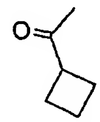
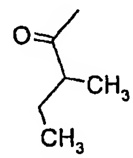
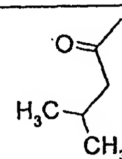
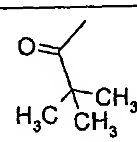
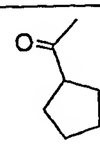
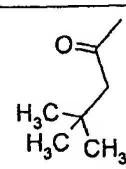
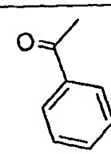
Example	Reagent	R	Measured Mass (M+H)
467	None		377.2087
468	Isobutyryl chloride		447.2468
469	Cyclohexanecarbonyl chloride		487.2783
470	Phenylacetyl chloride		495.2465
471	4-Fluorobenzoyl chloride		499.2272
472	3-Methoxybenzoyl chloride		497.2263
473	1-Methylimidazole-4-sulfonyl chloride		521.2071
474	2,2,2-Trifluoroethanesulfonyl chloride		523.1717

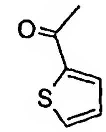
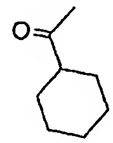
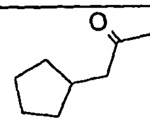
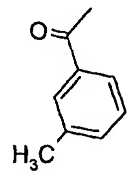
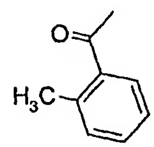
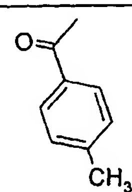
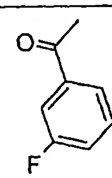
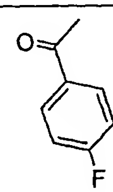
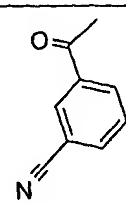
475	*alpha*-Toluenesulfonyl chloride		531.2134
476	3-Methoxybenzenesulfonyl chloride		533.1941
477	Isopropyl isocyanate		462.2611
478	3-Fluorophenyl isocyanate		514.2357

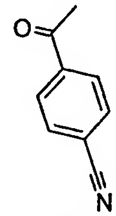
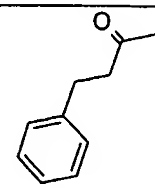
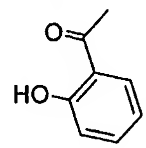
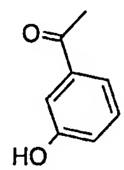
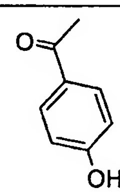
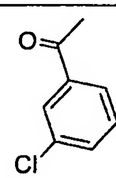
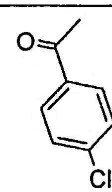
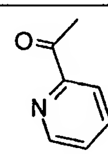
Examples 479 – 543

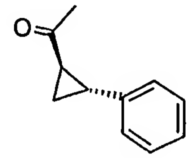
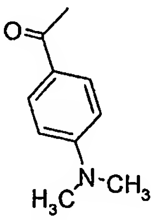
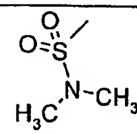
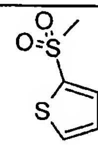
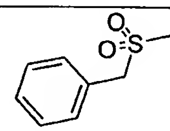
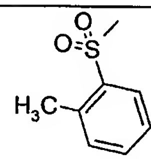
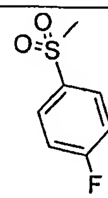
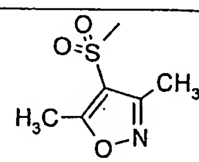
The compounds in the table below were prepared and purified according to the methods of Parts B and C of Examples 467 – 478 using 1-(4-benzylaminobutyl)-2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-4-amine in lieu of 2-methoxymethyl-1-{4-[(pyridin-3-ylmethyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine. 1-(4-Benzylaminobutyl)-2-ethoxymethy-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared according to the general method of Part A of Examples 467 – 478 using benzaldehyde in lieu of pyridine 3-carboxaldehyde and 1-(4-aminobutyl)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine in lieu of 1-(4-aminobutyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

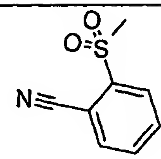
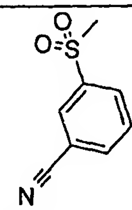
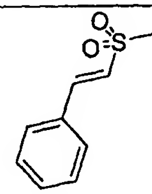
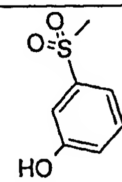
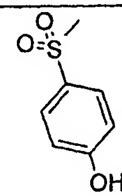
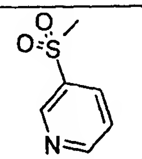
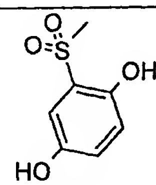
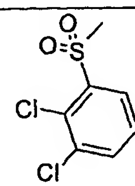


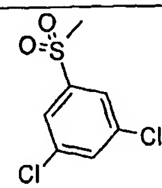
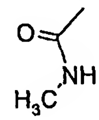
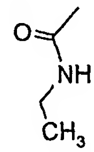
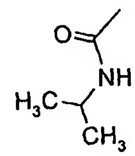
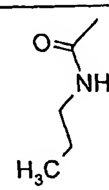
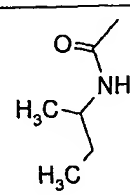
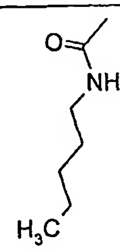
Example	Reagent	R	Measured Mass (M+H)
479	Cyclobutanecarbonyl chloride		458.2550
480	*DL*-2-Methylbutyryl chloride		460.2707
481	Isovaleryl chloride		460.2714
482	Pentanoyl chloride		460.2730
483	Pivaloyl chloride		460.2714
484	Cyclopentanecarbonyl chloride		472.2712
485	*tert*-Butylacetyl chloride		474.2879
486	Benzoyl chloride		480.2398

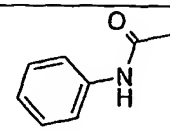
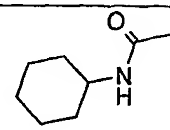
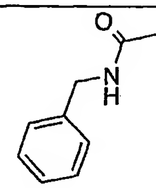
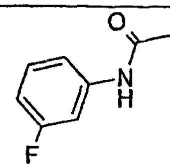
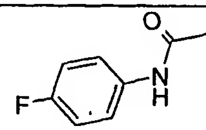
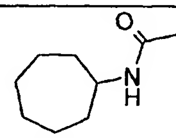
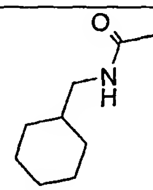
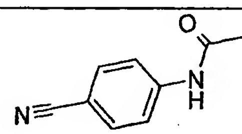
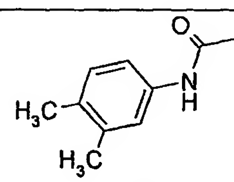
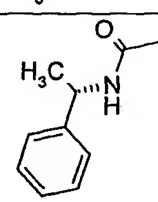
487	Thiophene-2-carbonyl chloride		486.1971
488	Cyclohexanecarbonyl chloride		486.2893
489	Cyclopentylacetyl chloride		486.2818
490	*m*-Toluoyl chloride		494.2577
491	*o*-Toluoyl chloride		494.2531
492	*p*-Toluoyl chloride		494.2527
493	3-Fluorobenzoyl chloride		498.2307
494	4-Fluorobenzoyl chloride		498.2326
495	3-Cyanobenzoyl chloride		505.2378

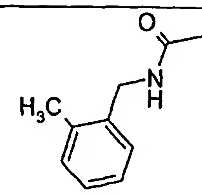
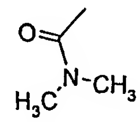
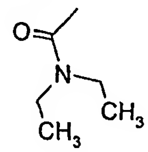
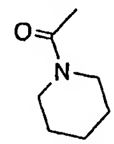
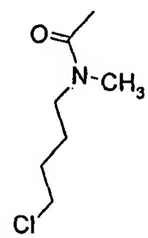
496	4-Cyanobenzoyl chloride		505.2387
497	Hydrocinnamoyl chloride		508.2715
498	2-Methoxybenzoyl chloride		496.2311
499	3-Methoxybenzoyl chloride		496.2314
500	*p*-Anisoyl chloride		496.2365
501	3-Chlorobenzoyl chloride		514.2026
502	4-Chlorobenzoyl chloride		514.2041
503	Picolinoyl chloride hydrochloride		481.2361

504	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		520.2695
505	4-Dimethylaminobenzoyl chloride		523.2802
506	1-Propanesulfonyl chloride		482.2232
507	Dimethylsulfamoyl chloride		483.2196
508	2-Thiophenesulfonyl chloride		522.1613
509	*alpha*-Toluenesulfonyl chloride		530.2239
510	*o*-Toluenesulfonyl chloride		530.2197
511	4-Fluorobenzenesulfonyl chloride		534.2028
512	3,5-Dimethylisoxazole-4-sulfonyl chloride		535.2106

513	2-Cyanobenzenesulfonyl chloride		541.1968
514	3-Cyanobenzenesulfonyl chloride		541.2035
515	*beta*-Styrene sulfonyl chloride		542.2234
516	3-Methoxybenzenesulfonyl chloride		532.2052
517	4-Methoxybenzenesulfonyl chloride		532.2037
518	3-Pyridine sulfonyl chloride hydrochloride		517.2015
519	2,5-Dimethoxybenzenesulfonyl chloride		548.1964
520	2,3-Dichlorobenzenesulfonyl chloride		584.1294

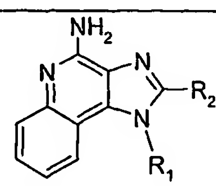
521	3,5-Dichlorobenzenesulfonyl chloride		584.1282
522	Methyl isocyanate		433.2361
523	Ethyl isocyanate		447.2538
524	Isopropyl isocyanate		461.2663
525	*n*-Propyl isocyanate		461.2691
526	*n*-Butyl isocyanate		475.2860
527	*sec*-Butyl isocyanate		475.2849
528	Pentyl isocyanate		489.3005

529	Phenyl isocyanate		495.2511
530	Cyclohexyl isocyanate		501.2978
531	Benzyl isocyanate		509.2675
532	3-Fluorophenyl isocyanate		513.2467
533	4-Fluorophenyl isocyanate		513.2388
534	Cycloheptyl isocyanate		515.3081
535	Cyclohexanemethyl isocyanate		515.3163
536	4-Cyanophenyl isocyanate		520.2483
537	3,4-Dimethylphenyl isocyanate		523.2786
538	(*S*)-(-)-*alpha*-Methylbenzyl isocyanate		523.2786

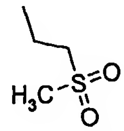
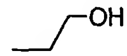
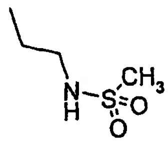
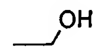
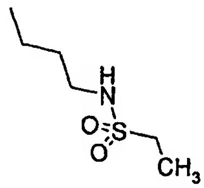
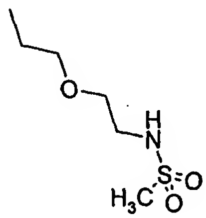
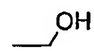
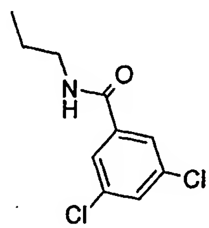
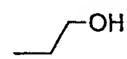
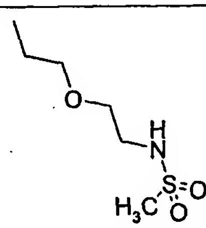
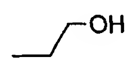
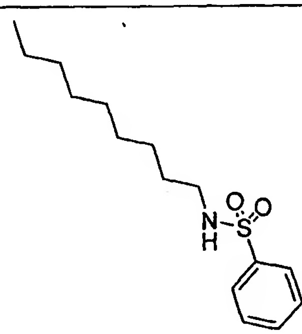
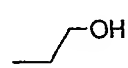
539	2-Methylbenzyl isocyanate		523.2860
540	*N*,*N*-Dimethylcarbamoyl chloride		447.2511
541	Diethylcarbamyl chloride		475.2828
542	1-Piperidinecarbonyl chloride		487.2839
543	*N*-(4-Chlorobutyl)-*N*-methylcarbamyl chloride		523.2588

Examples 544 – 550

The compounds in the table below were prepared according to the general method of Examples 111 – 140. The table shows a reference for the ether starting material, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



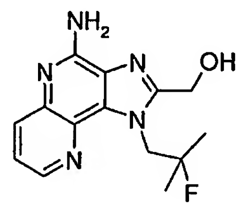
Example	Reference (ether)	R_1	R_2	Measured Mass (M+H)

544	U.S. Patent No. 6,667,312*			335.1158
545	U.S. Patent No. 6,677,349*			336.1098
546	U.S. Patent No. 6,677,349*			364.1454
547	U.S. Patent No. 6,677,347 Example 57			380.1391
548	U.S. Patent No. 6,756,382*			444.0999
549	U.S. Patent No. 6,683,088 Example 1			394.1588
550	U.S. Patent No. 6,677,349 Example 242			496.2401

*Although not specifically exemplified, the compound is readily prepared using the disclosed synthetic methods.

Example 551

[4-Amino-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol



Part A

A solution of 1-amino-2-methylpropan-2-ol (23.4 g, 263 mmol) dissolved in 150 mL of THF was treated with 150 mL of 1.8 M aqueous NaOH solution and the mixture was placed in an ice bath. A solution of di-*tert*-butyl dicarbonate (57.3 g, 263 mmol) in 150 mL THF was then added drop-wise over 45 min. The mixture was allowed to warm to ambient temperature overnight. The THF was removed under reduced pressure and the remaining aqueous solution was treated with 1 M H_2SO_4 until the pH reached 3. The mixture was extracted with 200 mL of EtOAc. The organic portion was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure give *tert*-butyl 2-hydroxy-2-methylpropylcarbamate (50.4 g) as a colorless syrup which solidified on standing.

Part B

A stirred solution of *tert*-butyl 2-hydroxy-2-methylpropylcarbamate (7.81 g, 41.3 mmol) dissolved in 300 mL of anhydrous CH_2Cl_2 was cooled to -78 °C under an atmosphere of N_2. The reaction mixture was treated with diethylaminosulfur trifloride (DAST) (6.2 mL, 47 mmol) and allowed to warm to ambient temperature overnight. The reaction mixture was treated with saturated $NaHCO_3$ solution and the layers were separated. The organic portion was washed successively with saturated $NaHCO_3$ solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 10% EtOAc/hexanes) gave 6.27 g of *tert*-butyl 2-fluoro-2-methylpropylcarbamate as an amber oil which solidified on standing.

Part C

tert-Butyl 2-fluoro-2-methylpropylcarbamate (6.27 g, 32.8 mmol) was treated with 45 mL of 3.0 M HCl in ethanol and the mixture was heated to 90 °C for 2 hours. The reaction mixture was then concentrated under reduced pressure to give 4.02 g of 2-fluoro-2-methylpropan-1-amine hydrochloride as a white solid.

Part D

2-Fluoro-2-methylpropan-1-amine hydrochloride (4.02 g, 31.4 mmol) was dissolved in 80 mL of dry CH_2Cl_2. Triethylamine (13.1 mL, 94.2 mmol) and 4-chloro-3-nitro[1,5]naphthyridine (6.56 g, 31.4 mmol) were then added and the reaction was stirred under N_2 for 2 days. The reaction mixture was then concentrated under reduced pressure to give a dark-yellow solid. The solid was treated with 200 mL of H_2O and the mixture was heated to reflux with rapid stirring. The mixture was cooled and the yellow solid was isolated by filtration. The material was washed with H_2O and the dried under vacuum to give *N*-(2-fluoro-2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (8.36 g) as a yellow powder.

Part E

A solution of *N*-(2-fluoro-2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (2.64 g, 10.0 mmol) dissolved in 80 mL of acetonitrile was placed in a pressure bottle. Platinum on carbon (5%, 500 mg) was then added and the reaction mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa). After 5 hours, the reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with acetonitrile and the combined filtrates were concentrated under reduced pressure to give 2.12 g of N^4-(2-fluoro-2-methylpropyl)[1,5]naphthyridine-3,4-diamine as a brown foam.

Part F

N^4-(2-Fluoro-2-methylpropyl)[1,5]naphthyridine-3,4-diamine (2.12 g, 9.06 mmol) was dissolved in 90 mL of anhydrous CH_2Cl_2 and the stirred solution was cooled to 0 °C under N_2. Triethylamine (1.39 mL, 10.0 mmol) and acetoxyacetyl chloride (1.07 mL, 10.0 mmol) were then added and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the resulting material was dissolved in 90 mL of ethanol and treated with 5 mL of triethylamine. The mixture was heated at reflux for 4 days. The reaction mixture was then cooled and concentrated under reduced pressure to give a purple solid. The purple solid was partitioned between CH_2Cl_2 (75 mL)

and H_2O (75 mL). The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a purple solid. The resulting material was dissolved in 50 mL of methanol and treated with 1 mL of saturated aqueous K_2CO_3 solution. After 1 hour, the mixture was treated with 3.5% NaH_2PO_4 solution and the methanol was removed by evaporation under reduced pressure. A brown solid precipitated out of the aqueous solution and was isolated by filtration. The brown solid was rinsed with H_2O and then dried to give 1.81 g of [1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol.

Part G

A solution of [1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol (1.53 g, 5.58 mmol) dissolved in 50 mL of CH_2Cl_2 was treated with triethylamine (1.55 mL, 11.2 mmol), acetic anhydride (663 μL, 6.70 mmol), and 10 mg of 4-(dimethylamino)pyridine (DMAP). After stirring for 2 hours, the reaction mixture was treated with saturated $NaHCO_3$ solution and the layers were separated. The organic portion was washed successively with 3.5% NaH_2PO_4 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Chromatography (SiO_2, 40-60% acetone/hexanes) gave 1.59 g of [1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl acetate as an off-white powder.

Part H

[1-(2-Fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl acetate (1.59 g, 5.03 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with 3-chloroperoxybenzoic acid (1.52 g, 57-86% purity). After stirring for 2 hours, the reaction mixture was treated with 25 mL of CH_2Cl_2 and 20 mL of 5% Na_2CO_3 solution and the layers were separated. The organic layer was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1.67 g of [1-(2-fluoro-2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl acetate as an off-white solid.

Part I

[1-(2-Fluoro-2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl acetate (1.67 g, 5.03 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with

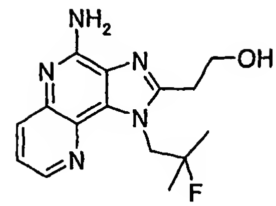
5 mL of concentrated aqueous NH_4OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (1.05 g, 5.53 mmol) was carefully added. Rapid stirring was continued for 1 hour. The reaction mixture was then treated with 20 mL of H_2O. The layers were separated and the organic portion was washed successively with 5% Na_2CO_3 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (SiO_2, 2.5% methanol/$CHCl_3$) gave 1.13 g of [4-amino-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl acetate as a light-yellow solid.

Part J

A solution of [4-amino-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methyl acetate (1.13 g, 3.41 mmol) dissolved in 10 mL of methanol was treated with 10 mL of a 7% solution of ammonia in methanol. The mixture was stirred for 2 hours and then concentrated under reduced pressure. The resulting solid was treated with H_2O and the mixture was heated to reflux for 15 minutes. The mixture was cooled and the resulting light-yellow solid was isolated by filtration. The light-yellow solid was then treated with 20 mL of CH_2Cl_2 and the mixture was stirred rapidly for several minutes. The mixture was filtered and the resulting white solid was washed with several portions of cold CH_2Cl_2 and dried with suction. Crystallization from ethanol/H_2O gave 477 mg of [4-amino-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol as fluffy cream colored crystals, mp 240 – 241 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (dd, J = 1.5, 4.3 Hz, 1H), 7.93 (dd, J = 1.5, 8.4 Hz, 1H), 7.46 (dd, J = 4.3, 8.4 Hz, 1H), 6.92 (s, 2H), 5.62 (t, J = 5.8 Hz, 1H), 5.33 (br s, 2H), 4.83 (d, J = 4.7 Hz, 2H), 1.33 (d, J = 20.3 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.3, 152.7, 143.1, 140.8, 134.2, 133.4, 133.2, 128.7, 122.5, 96.8 (d, J = 170 Hz), 56.7 (d, J = 9.5 Hz), 52.7 (d, J = 21.4 Hz), 24.5; MS (ESI) *m/z* 290 $(M + H)^+$; Anal. calcd for $C_{14}H_{16}FN_5O$: C, 58.12; H, 5.57; N, 24.21. Found: C, 58.19; H, 5.54; N, 24.16.

Example 552

2-[4-Amino-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]ethanol



Part A

N^4-(2-Fluoro-2-methylpropyl)[1,5]naphthyridine-3,4-diamine (2.34 g, 10.0 mmol) was dissolved in 80 mL of anhydrous CH_2Cl_2 and the stirred solution was cooled to 0 °C under N_2. Triethylamine (2.78 mL, 10.0 mmol) and 3-(benzyloxy)propanoyl chloride, prepared by the method of Li, *J. Med. Chem.*, 42, pp. 706-721, (2.13 g, 10.0 mmol), were then added and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure. The resulting material was dissolved in 80 mL of ethanol and combined with 5 mL of triethylamine and the mixture was heated to reflux for 4 days. The reaction mixture was then cooled and concentrated under reduced pressure. The resulting solid was partitioned between CH_2Cl_2 (75 mL) and H_2O (75 mL). The layers were separated and the organic portion was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid. Chromatography (SiO_2, 1-2% CMA/$CHCl_3$) gave 0.83 g of uncyclized amide (3-(benzyloxy)-*N*-{4-[(2-fluoro-2-methylpropyl)amino][1,5]naphthyridin-3-yl}propanamide) and the desired 2-[2-(benzyloxy)ethyl]-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine. Additional chromatography (10% methanol/$CHCl_3$) of the desired material gave 1.39 g of a light-orange syrup. The isolated amide was converted to the desired imidazole by dissolving the material in 10 mL of 7% ammonia in methanol. The mixture was placed in a stainless-steel pressure vessel and the vessel was sealed and heated to 150 °C overnight. The reaction mixture was cooled and concentrated under reduced pressure. Chromatography (SiO_2, 2% CMA/$CHCl_3$) gave 0.50 g of the desired product which was combined with the first batch of material for the next reaction.

Part B

2-[2-(Benzyloxy)ethyl]-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (1.89 g, 5.0 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with 3-chloroperoxybenzoic acid (1.50 g, 57-86% purity). After stirring for 2 hours, the reaction mixture was treated with 50 mL of 2% Na_2CO_3 solution and the layers were separated. The aqueous portion was extracted with an additional 25 mL of CH_2Cl_2. The

combined organic layers were washed successively with 2% Na_2CO_3, H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1.97 g of 2-[2-(benzyloxy)ethyl]-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine 5-oxide as an off-white solid.

Part C

2-[2-(Benzyloxy)ethyl]-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine 5-oxide (1.97 g, 5.00 mmol) was dissolved in 50 mL of CH_2Cl_2 and treated with 5 mL of concentrated aqueous NH_4OH solution. The mixture was stirred rapidly and then *p*-toluenesulfonyl chloride (1.00 g, 5.33 mmol) was carefully added. Rapid stirring was continued for 1 hour. The reaction mixture was then treated with 20 mL of H_2O. The layers were separated and the organic portion was washed successively with 5% Na_2CO_3 solution, H_2O and brine. The organic portion was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Chromatography (SiO_2, 10% CMA/$CHCl_3$) gave 0.90 g of 2-[2-(benzyloxy)ethyl]-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a yellow solid.

Part D

A solution of 2-[2-(benzyloxy)ethyl]-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.78 g, 1.98 mmol) dissolved in 20 mL of methanol was treated with 10% palladium on carbon (200 mg) and 0.68 mL of 3 M HCl in ethanol. The mixture was shaken under H_2 at 50 PSI (3.4×10^5 Pa) overnight. Additional 10% palladium on carbon (200 mg) and 3 M HCl in ethanol (0.33 mL) were added and shaking was continued for 24 hours. The reaction mixture was filtered through a pad of CELITE filter agent. The pad was rinsed with methanol and the combined filtrates were concentrated under reduced pressure. The resulting material was treated with 20 mL of H_2O and 2 mL of concentrated NH_4OH solution and extracted into $CHCl_3$ (3 x 25 mL). The combined organic layers were concentrated under reduced pressure. Chromatography (SiO_2, 15-30% CMA/$CHCl_3$) gave a white powder. Crystallization from ethanol/H_2O gave 276 mg of 2-[4-amino-1-(2-fluoro-2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]ethanol as white needles, mp 224 – 225 °C.

^{1}H NMR (300 MHz, DMSO-d_6, 354 K) δ 8.470 (dd, J = 1.3, 4.0 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 4.1, 8.3 Hz, 1H), 6.46 (s, 2H), 5.25 (d, J = 22.7 Hz, 2H), 4.57 (s, 1H), 3.91 (d, J = 5.4 Hz, 2H), 3.14 (t, J = 6.4 Hz, 2H), 1.33 (d, J = 21.7 Hz, 6H); ^{13}C NMR

(125 MHz, DMSO-d_6) δ 154.0, 152.3, 143.0, 140.4, 134.1, 133.1, 132.6, 129.0, 122.2, 96.7 (d, J = 170 Hz), 60.2, 52.5 (d, J = 20.9 Hz), 30.6 (d, J = 6.6 Hz), 24.4; MS (ESI) *m/z* 304 $(M + H)^+$; Anal. calcd for $C_{15}H_{18}FN_5O$: C, 59.39; H, 5.98; N, 23.09. Found: C, 59.57; H, 5.75; N, 23.07.

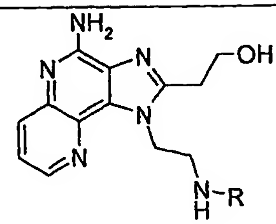
Examples 553 – 593

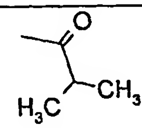
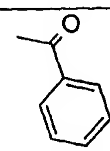
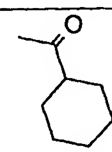
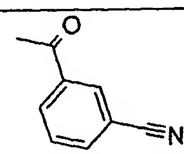
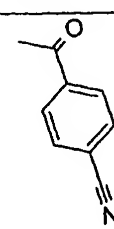
Part A

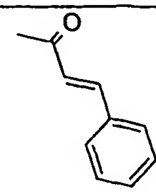
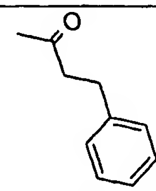
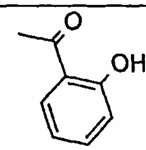
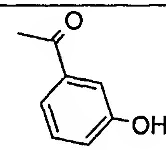
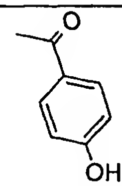
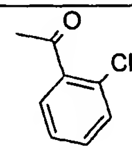
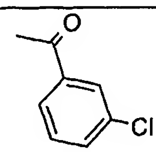
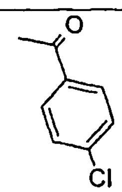
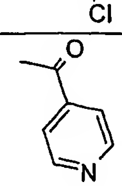
A solution of 1-(2-aminoethyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (57 mg, 0.1 mmol, 1 eq, prepared according to the general method of Example 146 using methoxypropionyl chloride in lieu of methoxyacetyl chloride) and *N,N*-diisopropylethylamine (87 µL) in *N, N*-dimethylacetamide (1 mL) was added to a tube containing a reagent (1.1 eq) from the table below. The reaction mixture was vortexed overnight, the reaction was quenched with water (2 drops), and the solvent was removed by vacuum centrifugation. The reaction mixture was purified by solid-supported liquid-liquid extraction according to the following procedure. The sample was dissolved in chloroform (1 mL) then loaded onto diatomaceous earth that had been equilibrated with 2 M sodium carbonate solution (600 µL) for about 20 minutes. After 10 minutes chloroform (500 µL) was added to elute the product from the diatomaceous earth into a well of a collection plate. After an additional 10 minutes the process was repeated with additional chloroform (500 µL). The solvent was then removed by vacuum centrifugation.

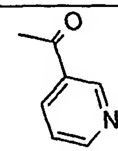
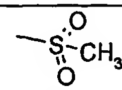
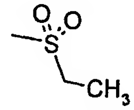
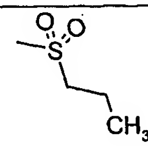
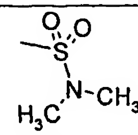
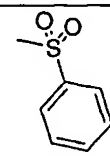
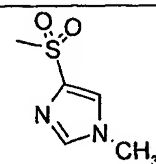
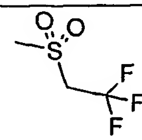
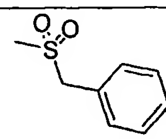
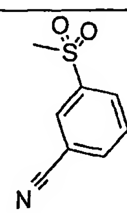
Part B

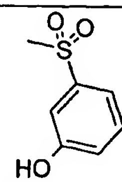
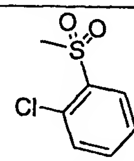
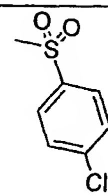
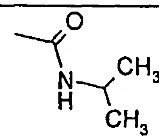
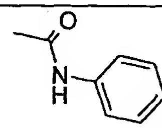
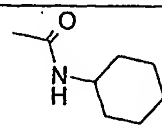
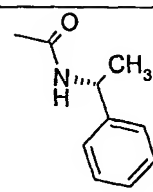
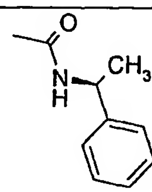
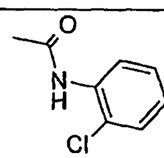
The material from Part A was dissolved in dichloromethane (1 mL) and the solution was cooled to 0 °C. Boron tribromide (400 µL of 1 M in dichloromethane) was added and the reaction mixture was vortexed overnight. Methanol (1 mL) and 6 N hydrochloric acid (500 µL) were added and the reaction mixture was vortexed for 15 minutes. The solvent was removed by vacuum. The compounds were purified as described for Examples 150 – 155. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

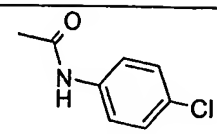
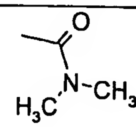
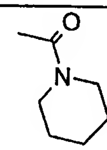
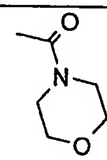


Example	Reagent	R	Measured Mass (M+H)
553	None	—H	273.1479
554	Cyclopropanecarbonyl chloride		341.1730
555	Isobutyryl chloride		343.1909
556	Cyclobutanecarbonyl chloride		355.1909
557	Cyclopentanecarbonyl chloride		369.2062
558	Benzoyl chloride		377.1747
559	Cyclohexanecarbonyl chloride		383.2206
560	3-Cyanobenzoyl chloride		402.1702
561	4-Cyanobenzoyl chloride		402.1700

562	Cinnamoyl chloride		403.1890
563	Hydrocinnamoyl chloride		405.2044
564	2-Methoxybenzoyl chloride		393.1672
565	3-Methoxybenzoyl chloride		393.1689
566	*p*-Anisoyl chloride		393.1678
567	2-Chlorobenzoyl chloride		411.1306
568	3-Chlorobenzoyl chloride		411.1369
569	4-Chlorobenzoyl chloride		411.1368
570	Isonicotinoyl chloride hydrochloride		378.1698

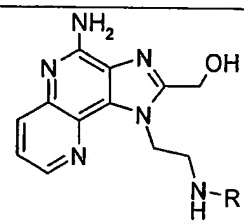
571	Nicotinoyl chloride hydrochloride		378.1676
572	Methanesulfonyl chloride		351.1256
573	Ethanesulfonyl chloride		365.1386
574	1-Propanesulfonyl chloride		379.1534
575	Dimethylsulfamoyl chloride		380.1512
576	Benzenesulfonyl chloride		413.1436
577	1-Methylimidazole-4-sulfonyl chloride		417.1462
578	2,2,2-Trifluoroethanesulfonyl chloride		419.1139
579	*alpha*-Toluenesulfonyl chloride		427.1569
580	3-Cyanobenzenesulfonyl chloride		438.1380

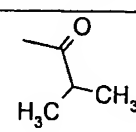
581	3-Methoxybenzenesulfonyl chloride		429.1349
582	2-Chlorobenzenesulfonyl chloride		447.0996
583	4-Chlorobenzenesulfonyl chloride		447.1031
584	Isopropyl isocyanate		358.1994
585	Phenyl isocyanate		392.1794
586	Cyclohexyl isocyanate		398.2305
587	(*R*)-(+)-*alpha*-Methylbenzyl isocyanate		420.2178
588	(*S*)-(-)-*alpha*-Methylbenzyl isocyanate		420.2149
589	2-Chlorophenyl isocyanate		426.1453

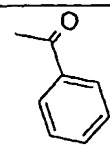
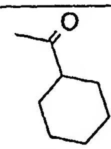
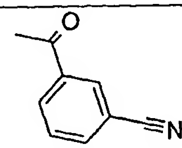
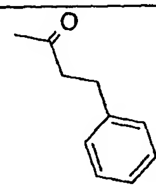
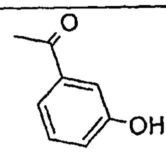
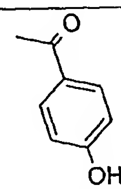
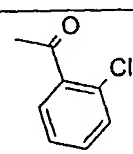
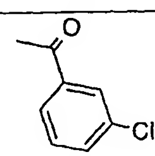
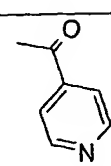
590	4-Chlorophenyl isocyanate		426.1460
591	*N,N*-Dimethylcarbamoyl chloride		344.1856
592	1-Piperidinecarbonyl chloride		384.2137
593	4-Morpholinylcarbonyl chloride		386.1976

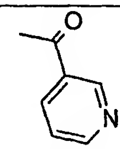
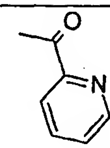
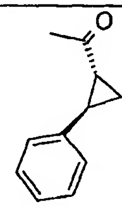
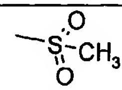
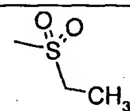
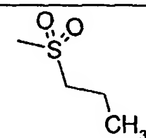
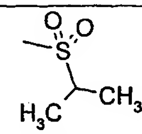
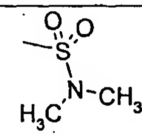
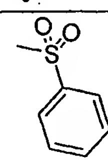
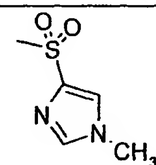
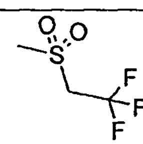
Examples 594 – 632

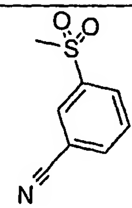
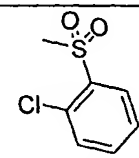
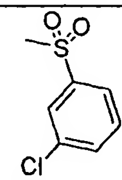
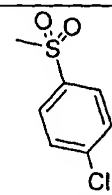
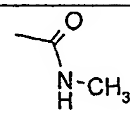
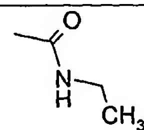
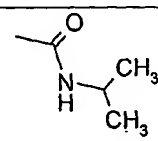
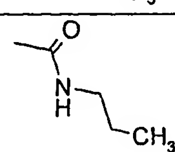
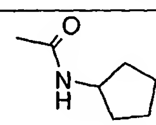
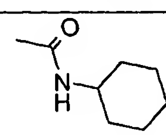
The compounds in the table below were prepared and purified according to the methods described in Examples 553 – 593 using 1-(2-aminoethyl)-2-methoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine in lieu of 1-(2-aminoethyl)-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

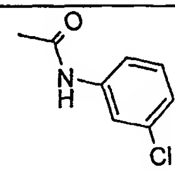
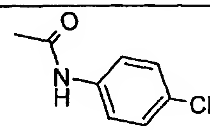
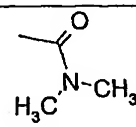
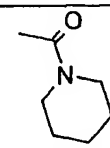
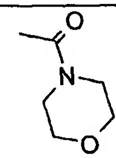
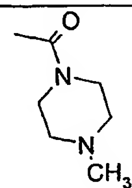


Example	Reagent	R	Measured Mass (M+H)
594	Cyclopropanecarbonyl chloride		327.1581
595	Isobutyryl chloride		329.1709

596	Cyclopentanecarbonyl chloride		355.1859
597	Benzoyl chloride		363.1563
598	Cyclohexanecarbonyl chloride		369.2019
599	3-Cyanobenzoyl chloride		388.1517
600	Hydrocinnamoyl chloride		391.1868
601	3-Methoxybenzoyl chloride		379.1512
602	*p*-Anisoyl chloride		379.1526
603	2-Chlorobenzoyl chloride		397.1193
604	3-Chlorobenzoyl chloride		397.1198
605	Isonicotinoyl chloride hydrochloride		364.1515

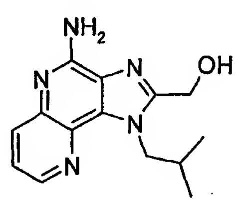
606	Nicotinoyl chloride hydrochloride		364.1535
607	Picolinoyl chloride hydrochloride		364.1512
608	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		403.1852
609	Methanesulfonyl chloride		337.1070
610	Ethanesulfonyl chloride		351.1212
611	1-Propanesulfonyl chloride		365.1386
612	Isopropylsulfonyl chloride		365.1433
613	Dimethylsulfamoyl chloride		366.1355
614	Benzenesulfonyl chloride		399.1214
615	1-Methylimidazole-4-sulfonyl chloride		403.1311
616	2,2,2-Trifluoroethanesulfonyl chloride		405.0953

617	3-Cyanobenzenesulfonyl chloride		424.1229
618	2-Chlorobenzenesulfonyl chloride		433.0872
619	3-Chlorobenzenesulfonyl chloride		433.0867
620	4-Chlorobenzenesulfonyl chloride		433.0853
621	Methyl isocyanate		316.1528
622	Ethyl isocyanate		330.1660
623	Isopropyl isocyanate		344.1819
624	*n*-Propyl isocyanate		344.1809
625	Cyclopentyl isocyanate		370.1994
626	Cyclohexyl isocyanate		384.2152

627	3-Chlorophenyl isocyanate		412.1300
628	4-Chlorophenyl isocyanate		412.1273
629	*N,N*-Dimethylcarbamoyl chloride		330.1686
630	1-Piperidinecarbonyl chloride		370.1979
631	4-Morpholinylcarbonyl chloride		372.1811
632	4-Methyl-1-piperazinecarbonyl chloride		385.2098

Example 633

[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol



To a chilled solution (ice bath) of 2-(ethoxymethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (2.0 g, 6.69 mmol, prepared according to the general methods of Example 148 using 2-methylpropan-1-amine in lieu of 1-amino-2-methylpropan-2-ol) in dichloromethane (50 mL) was added boron tribromide (20 mL, 1M solution in dichloromethane). The mixture turned light purple and was stirred at ambient temperature for 44 hours. The reaction was quenched with methanol (20 mL) and aqueous

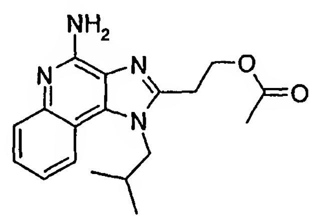
hydrochloric acid (6N, 10 mL). After stirring for 4 hours, the pH was adjusted to 10 by the addition of aqueous sodium hydroxide (50%). Dichloromethane (50 mL) was added with stirring and the layers were separated. The aqueous fraction was extracted with chloroform (2x 250 mL). The combined organic fractions were concentrated to provide 1.4 g of [4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methanol as a white powder, mp 226-228 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52-8.51 (dd, J = 1.6, 4.3 Hz, 1H), 7.93-7.89 (dd, J = 1.6, 8.4 Hz, 1H), 7.46-7.42 (dd, J = 4.3, 8.4 Hz, 1H), 6.83 (s, 2H), 5.69-5.65 (t, J = 5.8 Hz, 1H), 4.79-4.77 (d, J = 5.8 Hz, 2H), 4.74-4.71 (d, J = 7.6 Hz, 2H), 2.44-2.39 (m, 1H), 0.91-0.88 (d, J = 6.7 Hz, 6H);

Anal. calcd for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.31; N, 25.81. Found: C, 61.26; H, 6.07; N, 25.75.

Example 634

2-(4-Amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-2-yl)ethyl acetate



Part A

To a stirred suspension of N^4-isobutylquinoline-3,4-diamine (13.0 g, 60.46 mmol) in toluene was added pyridine hydrochloride (2.1 g, 8.14 mmol) followed by 3-chloropropionyl chloride (1.1 equivalents). The creamy suspension was stirred for 4 hours at ambient temperature and the solvent was then evaporated under reduced pressure. The tan solid obtained was dissolved in chloroform and the solution was transferred to a separatory funnel. The organic layer was washed with water (1x) and brine (2x). The organic layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure to afford a tan solid (21 g). A portion of the tan solid (7 g) was taken up in acetic acid (110 mL) and the reaction was stirred at ambient temperature for 4 hours. The reaction was cooled in an ice-bath and 6M NaOH (300 mL) was added in portions to afford a creamy suspension. The reaction mixture was transferred to a separatory funnel and the product was extracted with chloroform (150 mL x 2). The

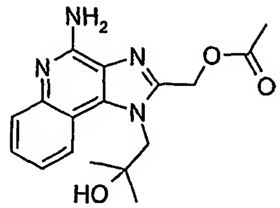
organic layers were combined, dried ($MgSO_4$), and filtered; and the filtrate was evaporated under reduced pressure to afford 2-(1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-2-yl)ethyl acetate as a brown oil (10 g) which was taken forward to the next step.

Part B

To a stirred solution of 2-(1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-2-yl)ethyl acetate (7.41 g, 22.9 mmol) in chloroform was added 3-chloroperoxybenzoic acid (77%, 10.3 g, 49.9 mmol) and the reaction was stirred at ambient temperature for 4 hours. The reaction was then transferred to a separatory funnel and washed with brine (2 x). The organic layers were combined, dried ($MgSO_4$), and filtered; and the filtrate was evaporated under reduced pressure to afford the N-oxide (15 g) as a brown solid. The brown solid was dissolved in chloroform, cooled in an ice-bath, and trichloroacetyl isocyanate (6.4 g mL, 34.3 mmol) was added in a dropwise manner. The reaction was stirred for 1 hour after which an additional 1.5 equivalents of trichloroacetyl isocyanate was added and the reaction was stirred at ambient temperature overnight. The reaction was concentrated under reduced pressure and the residue was suspended in ethanol. Potassium ethoxide was added to this suspension and the reaction was stirred for 1 hour. The reaction was concentrated under reduced pressure, taken up in dichloromethane (250 mL) and transferred to a separatory funnel. The organic layer was washed with water (250 mL), separated from the aqueous, dried ($MgSO_4$), and filtered; and the filtrate was evaporated under reduced pressure to afford a brown solid. The product was isolated by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of 0-10% methanol in dichloromethane with 1% ammonium hydroxide) to provide a solid (about 7g). A portion of this solid was recrystallized from acetonitrile to afford 2-(4-amino-1-isobutyl-1*H*-imidazo[4,5-*c*]quinolin-2-yl)ethyl acetate as a white solid (0.109 g), mp 187-189°C; MS (ESI) *m/z* 327 (M+H); Anal. Calcd for $C_{18}H_{22}N_4O_2 \cdot 0.40H_2O$: C, 64.81; H, 6.89; N, 16.79; Found C, 64.54; H, 6.46; N, 16.90.

Example 635

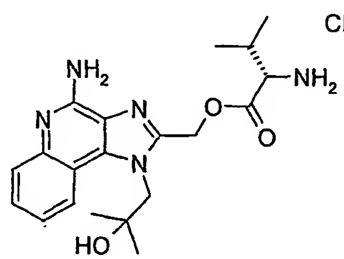
[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl acetate



To a round-bottomed flask with stir bar was added 1-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol (1 g, 3.5 mmol) followed by dichloroethane (20 mL) and pyridine (3 mL). To the stirred suspension was added acetyl chloride (0.27 mL, 1.1 equivalents) and the reaction was stirred at ambient temperature for 30 min. The solvent was evaporated under reduced pressure to afford a solid. The product was isolated by two purifications by prep HPLC (ISCO Combiflash Separation System, Biotage Si 40+M column, eluted with a gradient of 0-7% methanol in dichloromethane with 1% ammonium hydroxide) to provide [4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl acetate as an off white solid (130 mg), mp 203-205°C; MS (ESI) *m/z* 329 (M+H); Anal. Calcd for $C_{17}H_{20}N_4O_3{\bullet}0.25CH_4O$: C, 61.59; H, 6.29; N, 16.66; Found C, 61.24; H, 6.22; N, 16.97.

Example 636

[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl L-valinate

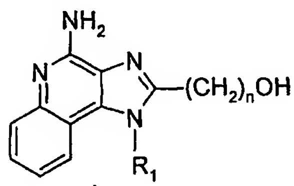


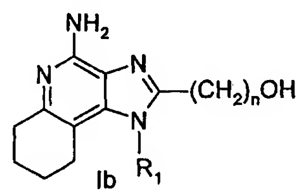
[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl L-valinate was prepared according to the general method used to prepare (4-amino-1-{4-{(methylsulfonyl)amino]butyl}-1*H*-imidazo[4,5-*c*]quinolin-2-yl)methyl L-valinate using 1-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol in lieu of *N*-[4-(4-amino-2-hydroxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide. The product was provided as off-white needles, mp 190-

192°C; MS (ESI) *m/z* 386 (M+H); Anal. Calcd for $C_{20}H_{27}N_5O_3$: C, 62.32; H, 7.06; N, 18.17; Found C, 62.08; H, 7.11; N, 17.96.

Exemplary Compounds Useful in Practicing Methods of the Invention

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Im, In, Io, or Ip and the following substituents n and R_1 wherein each line of the table is matched to Formula Ia, Ib, Ic, Id, Ie, If, Ig, Ih, Ii, Ij, Ik, Im, In, Io, or Ip to represent a specific compound which is useful in practicing methods of the invention.


Ia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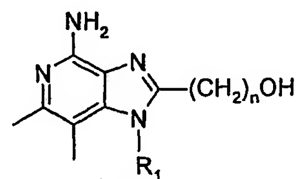
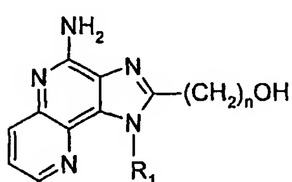
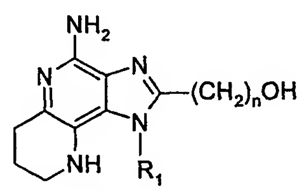

Ic


Id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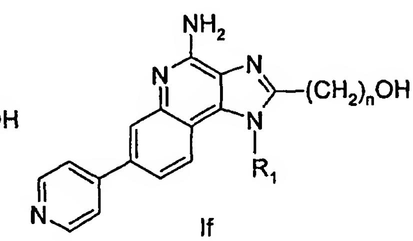
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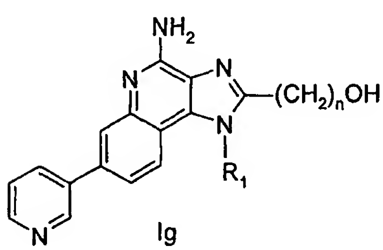
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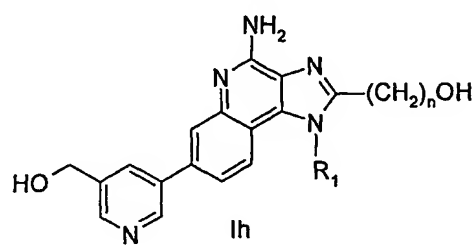
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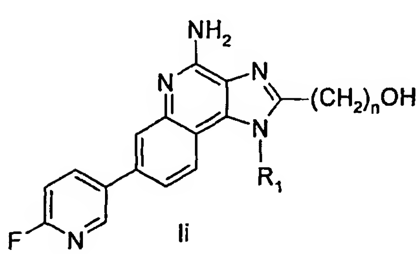
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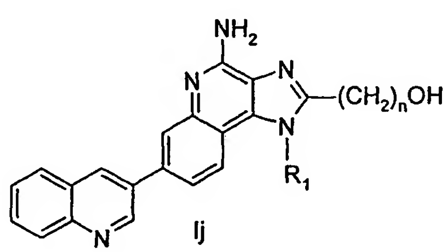
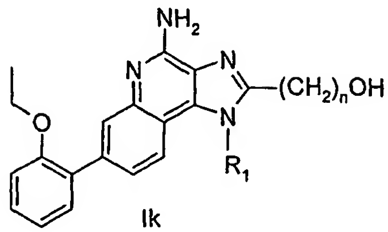
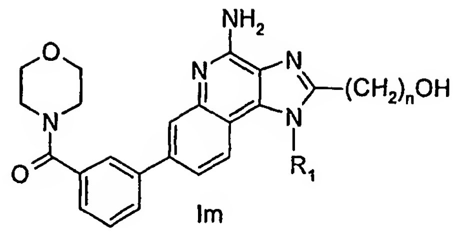

Ij



Ik



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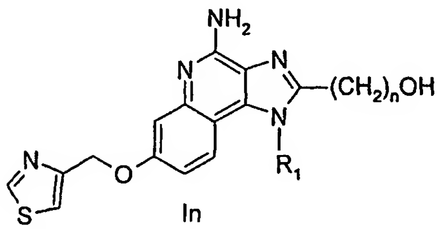
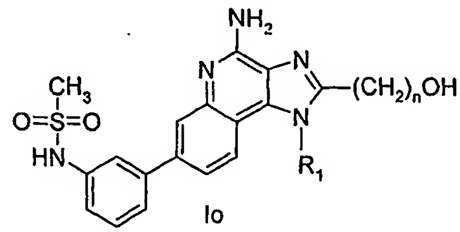
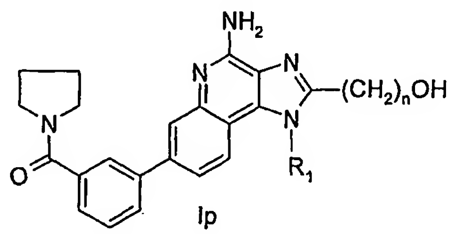


In



Io



Ip

n	R_1
1	2-[(cyclohexylcarbonyl)amino]-2-methylpropyl
1	2-[(cyclopropylcarbonyl)amino]ethyl
1	4-[(cyclopropylcarbonyl)amino]butyl
1	2,3-dihydroxypropyl
1	2,2-dimethyl-3-(methylsulfonyl)propyl
1	2-fluoro-2-methylpropyl
1	2-hydroxy-2-methylpropyl
1	2-methylpropyl
1	2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl
1	2-{[(1-methylethyl)carbonyl]amino}ethyl
1	4-{[(1-methylethyl)carbonyl]amino}butyl
1	2-methyl-2-[(methylsulfonyl)amino]propyl
1	4-[(methylsulfonyl)amino]butyl
1	2-[(methylsulfonyl)amino]ethyl
1	4-[(4-morpholinecarbonyl)amino]butyl

1	2-[(4-morpholinecarbonyl)amino]ethyl
1	tetrahydro-2*H*-pyran-4-ylmethyl
1	(4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl
1	(1-hydroxycyclobutyl)methyl
1	(1-hydroxycyclopentyl)methyl
1	(1-hydroxycyclohexyl)methyl
2	2-[(cyclohexylcarbonyl)amino]-2-methylpropyl
2	2-[(cyclopropylcarbonyl)amino]ethyl
2	4-[(cyclopropylcarbonyl)amino]butyl
2	2,3-dihydroxypropyl
2	2,2-dimethyl-3-(methylsulfonyl)propyl
2	2-fluoro-2-methylpropyl
2	2-hydroxy-2-methylpropyl
2	2-methylpropyl
2	2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl
2	2-{[(1-methylethyl)carbonyl]amino}ethyl
2	4-{[(1-methylethyl)carbonyl]amino}butyl
2	2-methyl-2-[(methylsulfonyl)amino]propyl
2	4-[(methylsulfonyl)amino]butyl
2	2-[(methylsulfonyl)amino]ethyl
2	4-[(4-morpholinecarbonyl)amino]butyl
2	2-[(4-morpholinecarbonyl)amino]ethyl
2	tetrahydro-2*H*-pyran-4-ylmethyl
2	(4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl
2	(1-hydroxycyclobutyl)methyl
2	(1-hydroxycyclopentyl)methyl
2	(1-hydroxycyclohexyl)methyl

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected and washed twice with DPBS or HBSS and re-suspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (usually 30-0.014 μM). The final concentration of PBMC suspension is 2 x

10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for IFN-α by ELISA and for TNF-α by IGEN/BioVeris Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis

IFN-α concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF-α concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF-α capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Assay Data and Analysis

In total, the data output of the assay consists of concentration values of TNF-α and IFN-α (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α) is subtracted from each reading. If any negative values result from background subtraction, the reading is reported as " * ", and is noted as not reliably detectable. In subsequent calculations and statistics, " * ", is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the

reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro-α,α-dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The minimum effective concentration (μmolar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN-α and 40 pg/mL for TNF-α). The maximal response (pg/mL) is the maximal response attained in the dose response curve.

Compounds used in the methods of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The analogs used are shown in the table below.

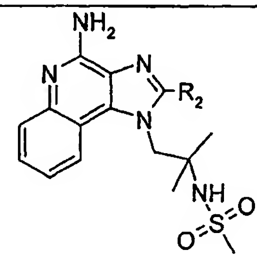
Analog	Chemical Name	Reference
1	*N*-[2-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349#
2	*N*-[2-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349#
3	*N*-[2-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349#
4	*N*-[2-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	U.S. Patent 6,677,349 Example 268
5	*N*-{2-[4-Amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide	Example 6 Part D

#This compound is not specifically exemplified but can be readily prepare using the synthetic methods disclosed in the cited reference

The compounds of Examples 6 and 7 and several closely related analogs were tested using the test method described above. The IFN-α dose response curves for Example 6, Analog 2, Analog 3 and Analog 5 are shown in Figure 1. The TNF-α dose response curves for Example 6, Analog 2, Analog 3 and Analog 5 are shown in Figure 2. The IFN-α dose response curves for Example 7, Analog 1, Analog 2 and Analog 4 are shown in Figure 3. The TNF-α dose response curves for Example 7, Analog 1, Analog 2 and Analog 4 are shown in Figure 4. The minimum effective concentration for the

induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 7 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

Table 7



Compound	R_2	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
		IFN	TNF	IFN	TNF	
Example 7	$-CH_2OH$	3.330	30.00	2250	121	5
Example 6	$-(CH_2)_2OH$	1.11	>30	7521	-	3
Analog 1	$-CH_3$	0.370	3.330	1846	1518	7
Analog 2	$-CH_2CH_3$	0.120	1.110	831	3670	4
Analog 3	$-(CH_2)_2CH_3$	0.120	0.370	832	7245	9
Analog 4	$-CH_2OCH_2CH_3$	0.040	0.370	889	10125	22
Analog 5	$-(CH_2)_2OCH_3$	0.014	0.12	825	12518	6

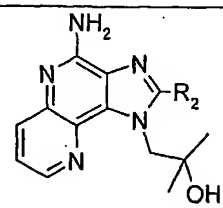
Further compounds used in the methods of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The analogs used are shown in the table below.

Analog	Chemical Name	Reference
6	1-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol	Example 148 Part E
7	1-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol	Example 149 Part J

The compounds of Examples 148 and 149 and several closely related analogs were tested using the test method described above. The IFN-α dose response curves for Example 148, Example 149, Analog 6, and Analog 7 are shown in Figure 5. The TNF-α

dose response curves for Example 148, Example 149, Analog 6, and Analog 7 are shown in Figure 6. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 8 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

Table 8



Compound	R_2	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
		IFN	TNF	IFN	TNF	
Example 148	$-CH_2OH$	1.11	10.0	3038	684	2
Example 149	$-(CH_2)_2OH$	3.33	30.0	1849	342	1
Analog 6	$-CH_2OCH_2CH_3$	0.12	1.11	658	4921	1
Analog 7	$-(CH_2)_2OCH_3$	0.04	0.37	4143	7762	1

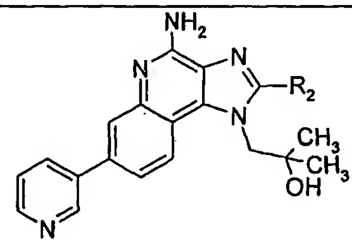
A further compound used in the methods of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The analogs used are shown in the table below.

Analog	Chemical Name	Reference
8	1-(4-amino-2-ethyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	U.S. Patent Publication 2004/0147543 Example 142
9	1-(4-amino-2-propyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	U.S. Patent Publication 2004/0147543 Example 418
10	1-(4-amino-2-ethoxymethyl-7-pyridin-3-yl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-2-methylpropan-2-ol	U.S. Patent Publication 2004/0147543 Example 126

The compound of Example 163 and several closely related analogs were tested using the test method described above. The IFN-α dose response curves are shown in

Figure 7. The TNF-α dose response curves are shown in Figure 8. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 9 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

Table 9

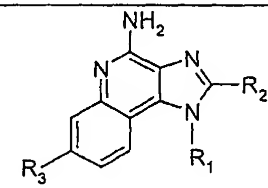


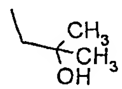
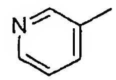
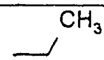
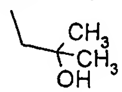
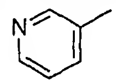
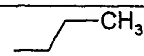
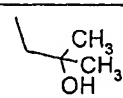
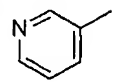
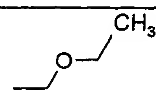
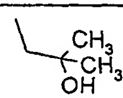
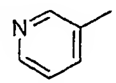
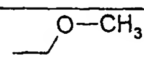
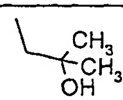
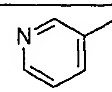
Compound	R_2	Minimum Effective Concentration (µM)		Maximal Response (pg/mL)		#
		IFN	TNF	IFN	TNF	
Example 163	$-CH_2OH$	1.11	>30	2251	*	1
Analog 8	$-CH_2CH_3$	0.12	0.37	1118	3234	4
Analog 9	$-(CH_2)_2CH_3$	0.04	0.37	597	3951	1
Analog 10	$-CH_2OCH_2CH_3$	0.04	0.12	840	0.12	5

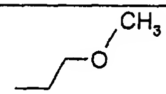
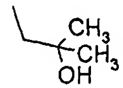
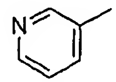
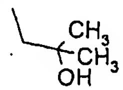
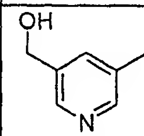
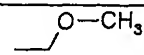
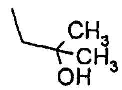
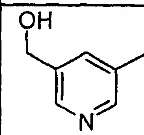
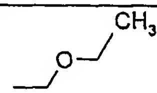
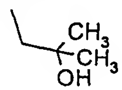
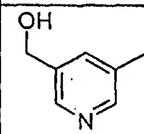
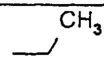
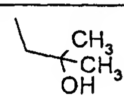
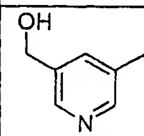
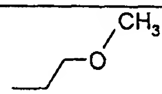
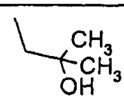
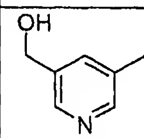
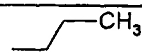
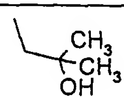
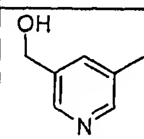
*Below experimental background level of 40 pg/mL.

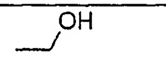
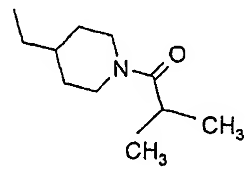
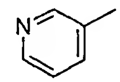
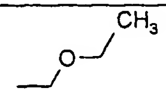
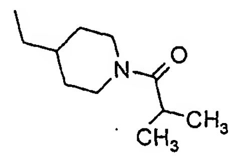
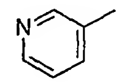
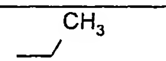
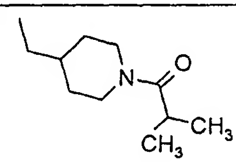
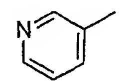
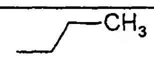
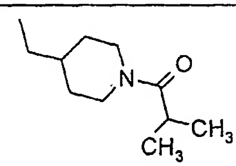
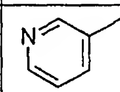
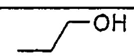
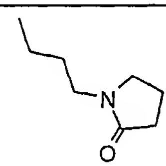
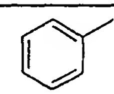
Compounds of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 10 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

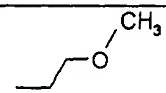
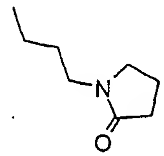
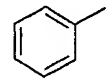
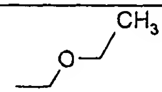
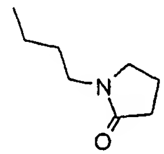
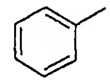
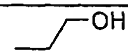
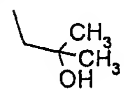
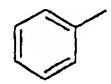
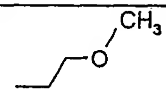
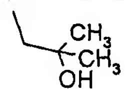
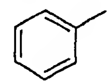
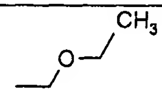
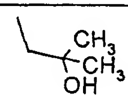
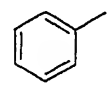
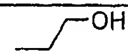
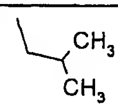
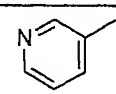
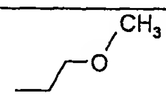
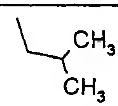
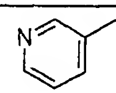
Table 10

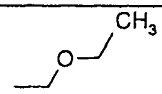
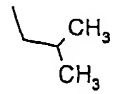
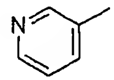
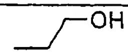
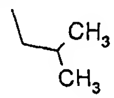
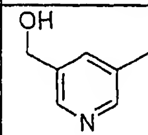
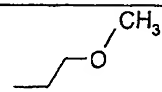
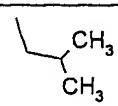
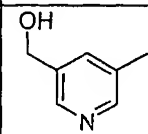
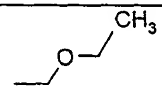
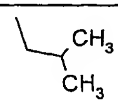
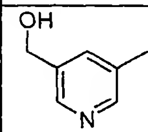
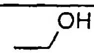
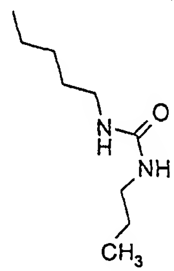
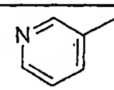


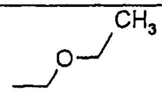
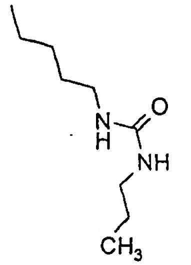
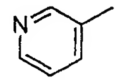
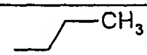
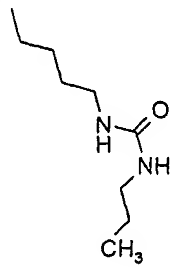
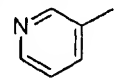
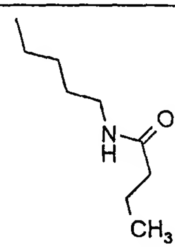
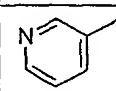
Compound	R_2	R_1	R_3	Minimum Effective Concentration (μM)		Maximal Response (pg/mL)		#
				IFN	TNF	IFN	TNF	
Example 163				0.37	10	2886	51	3
Analog 8				0.12	0.37	1652	3571	6
Analog 9				0.04	0.37	597	3951	1
Analog 10				0.04	0.12	840	7867	7
Analog 11				0.37	1.11	829	3445	4

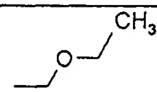
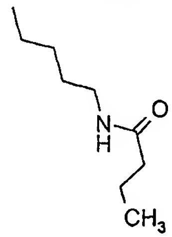
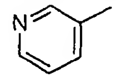
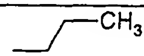
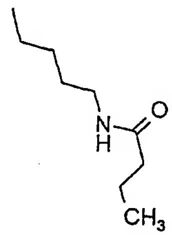
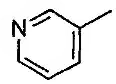
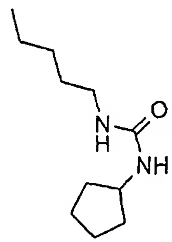
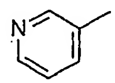
Analog 12				0.014	0.014	1065	8386	8
Example 189				0.37	>30	4357	*	3
Analog 13				0.12	3.33	1771	8000	4
Analog 14				0.014	0.12	6308	18284	4
Analog 15				0.014	1.11	2084	10087	5
Analog 16				0.014	0.04	5868	16296	2
Analog 17				0.014	0.12	1079	16482	2

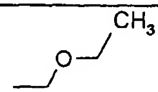
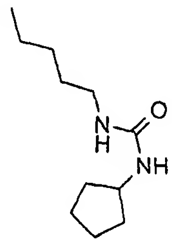
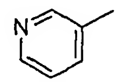
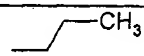
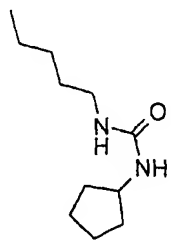
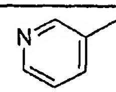
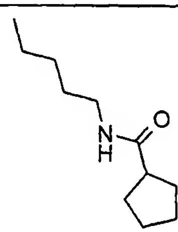
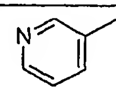
Example 191				1.11	>30	969	*	1
Analog 18				0.12	0.37	2979	1449	2
Analog 19				0.12	1.11	1686	619	8
Analog 20				0.12	0.37	1157	1054	2
Example 156				>30	>30	*	*	1

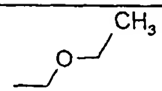
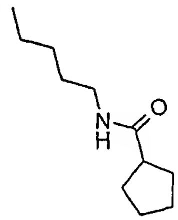
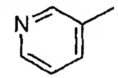
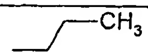
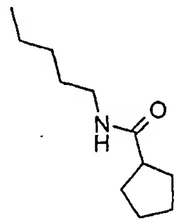
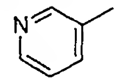
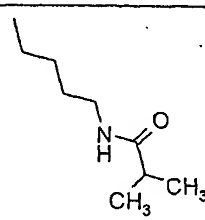
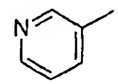
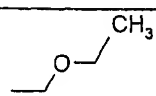
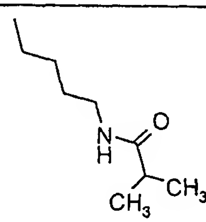
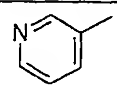
Analog 21				0.12	1.11	1880	201	2
Analog 22				0.37	1.11	1665	62	1
Example 157				0.37	3.33	1274	67	1
Analog 23				0.014	0.014	260	2296	1
Analog 24				0.014	0.12	440	2238	1
Example 158				0.37	3.33	1180	42	1
Analog 25				0.014	0.04	1199	3151	3

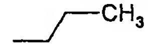
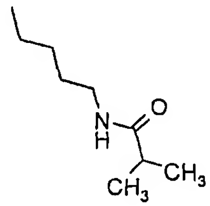
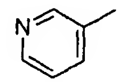
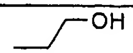
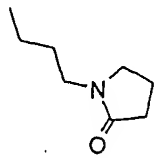
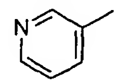
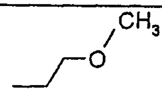
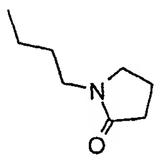
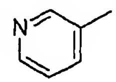
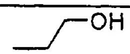
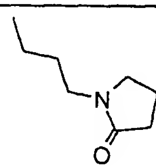
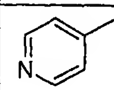
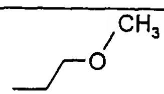
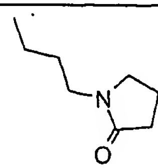
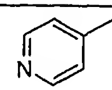
Analog 26				0.014	0.12	591	647	1
Example 159				0.12	10	1891	349	1
Analog 27				0.014	0.04	1332	9563	2
Analog 28				0.04	0.37	1263	3885	3
Example 195				0.37	30	5089	81	1

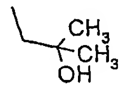
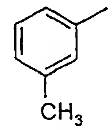
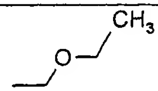
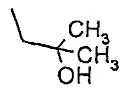
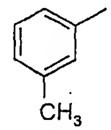
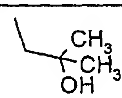
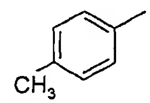
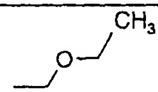
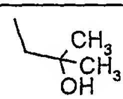
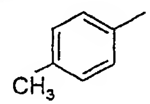
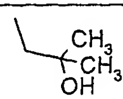
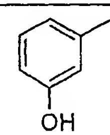
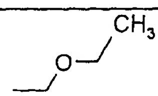
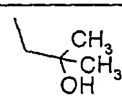
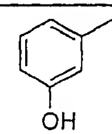
Analog 29				0.04	1.11	936	1059	2
Analog 30				0.37	0.37	531	5284	1
Example 196				0.12	>30	3516	*	1

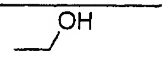
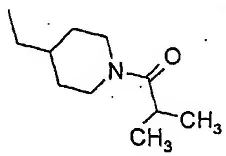
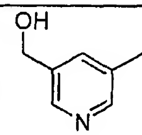
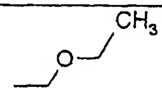
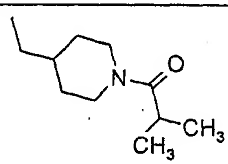
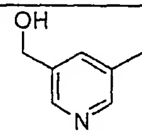
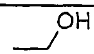
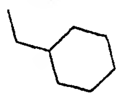
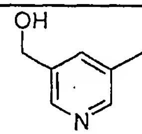
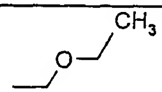
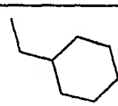
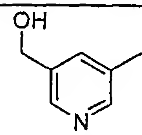
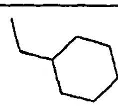
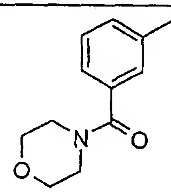
Analog 31				0.12	1.11	965	991	2
Analog 32				0.12	0.37	862	1647	2
Example 197				0.04	10	4373	600	1

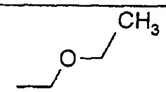
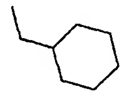
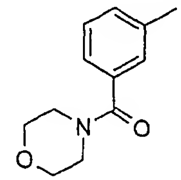
Analog 33				0.014	1.11	925	1618	2
Analog 34				0.014	0.37	649	9019	1
Example 198				0.12	3.33	2745	410	1

Analog 35				0.04	0.37	969	1366	2
Analog 36				0.12	0.37	521	2222	1
Example 199				0.37	10	5880	217	1
Analog 37				0.12	1.11	1194	728	2

Analog 38				0.12	0.37	1610	960	2
Example 160				30	>30	109	*	1
Analog 39				0.12	1.11	753	380	3
Example 161				>30	>30	*	*	1
Analog 40				0.37	3.33	1179	943	3

Example 164				30	>30	87	*	1
Analog 41				0.014	0.12	541	10184	1
Example 165				0.37	0.37	1681	7423	1
Analog 42				0.12	0.12	650	4456	1
Example 168				0.37	10	12641	352	1
Analog 43				0.04	0.04	740	3955	1

Example 201				>30	>30	*	*	1
Analog 44				0.04	1.11	1382	3128	1
Example 205				3.33	>30	1087	*	1
Analog 45				0.014	1.11	1062	2865	2
Example 206				1.11	>30	1266	*	1

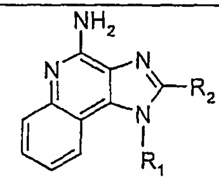
Analog 46				0.014	0.37	815	1054	1

*Below experimental background level

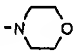
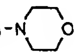
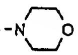
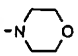
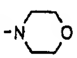
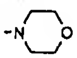
All analogs are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Application Publication 2004/0147543

Compounds of the invention and close analogs were tested for their ability to induce cytokine biosynthesis using the test method described above. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 11 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

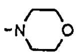
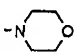
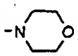
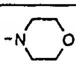
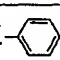
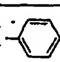
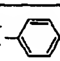
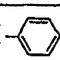
Table 11

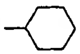
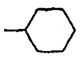
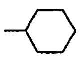
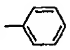
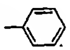
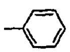
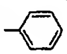
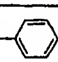


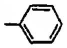
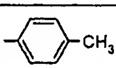
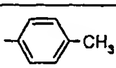
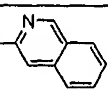
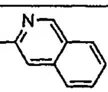
Compound	R_1	R_2	Minimum Effective Concentration (µM)		Maximal Response (pg/mL)		#
			IFN	TNF	IFN	TNF	
Example 7	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OH$	3.33	30	1670	154	6
Example 6	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	1.11	30	6527	*	4
Analog 1	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_3$	0.37	3.33	1846	1518	9
Analog 2	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2CH_3$	0.12	1.11	1096	9675	6
Analog 3	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	0.37	832	9780	11
Analog 4	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.04	0.37	1138	10665	33
Analog 5	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.12	1308	13908	8
Analog 47	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OCH_3$	0.37	3.33	1638	7151	1
Example 368	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2OH$	0.37	>30	7220	*	3
Example 3	$-(CH_2)_4NHS(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	2340	*	4
Analog 48	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_3$	0.12	10	7293	526	13
Analog 49	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2CH_3$	0.04	3.33	2712	679	79
Analog 50	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	1.11	2184	850	22
Analog 51	$-(CH_2)_4NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.04	1.11	2581	1439	10

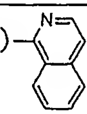
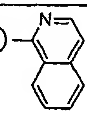
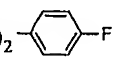
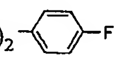
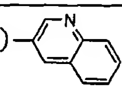
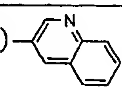
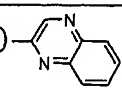
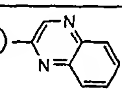
Analog 52	$-(CH_2)_4NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.37	7594	1931	13
Example 115	$-(CH_2)_4NHC(O)-$ 	$-(CH_2)_2OH$	1.11	>30	8361	*	1
Analog 53	$-(CH_2)_4NHC(O)-$ 	$-CH_3$	0.12	10	1538	1400	1
Analog 54	$-(CH_2)_4NHC(O)-$ 	$-CH_2CH_3$	0.37	3.33	4975	2570	1
Analog 55	$-(CH_2)_4NHC(O)-$ 	$-CH_2CH_2CH_3$	0.12	1.11	11255	1298	3
Analog 56	$-(CH_2)_4NHC(O)-$ 	$-CH_2OCH_2CH_3$	0.12	1.11	3433	1580	2
Analog 57	$-(CH_2)_4NHC(O)-$ 	$-(CH_2)_2OCH_3$	0.014	0.04	8889	3494	8
Example 122	$-(CH_2)_3NHS(O)_2CH_3$	$-(CH_2)_2OH$	3.33	>30	9651	*	3
Analog 58	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_3$	1.11	30	2778	*	11
Analog 59	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_2CH_3$	1.11	30	1912	238	2
Analog 60	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	1.11	10	2148	109	3
Analog 61	$-(CH_2)_3NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.37	10	1338	463	9
Analog 62	$-(CH_2)_3NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	1.11	3995	954	9
Example 131	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	8361	*	1
Analog 63	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_3$	0.37	10	1019	805	2
Analog 64	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_2CH_3$	0.12	3.33	1431	1453	3

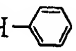
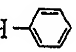
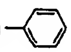
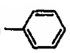
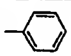
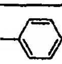
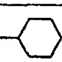
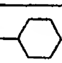
Analog 65	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	10	1711	1929	2
Analog 66	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.12	0.37	561	3768	5
Analog 67	$-CH_2C(CH_3)_2CH_2NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.04	1805	5467	10
Example 36	$-(CH_2)_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	10	>30	3316	*	1
Analog 68	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_3$	0.12	10	1610	820	3
Analog 69	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2CH_3$	0.12	10	3800	2401	6
Analog 70	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2CH_2CH_3$	30	10	2003	11432	2
Analog 71	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.12	3.33	1465	4918	9
Analog 72	$-(CH_2)_2NHS(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.04	5858	8547	6
Example 125	$-(CH_2)_5S(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	8361	*	1
Analog 73	$-(CH_2)_5S(O)_2CH_3$	$-CH_3$	0.37	3.33	1294	771	21
Analog 74	$-(CH_2)_5S(O)_2CH_3$	$-CH_2CH_3$	0.12	1.11	1062	1545	7
Analog 75	$-(CH_2)_5S(O)_2CH_3$	$-CH_2CH_2CH_3$	0.12	1.11	828	848	3
Analog 76	$-(CH_2)_5S(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	1.11	2695	6169	2
Example 133	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-(CH_2)_2OH$	0.37	>30	8361	*	1
Analog 77	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-CH_3$	0.12	1.11	1001	3571	1
Analog 78	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-CH_2CH_3$	0.12	1.11	1803	2525	1
Analog 79	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-CH_2CH_2CH_3$	0.37	3.33	1055	1312	2
Analog 80	$-(CH_2)_2O(CH_2)_2N(CH_3)S(O)_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.37	1630	2191	4
Example 99	$-(CH_2)_3NHC(O)NHCH(CH_3)_2$	$-(CH_2)_2OH$	0.37	>30	21829	*	1
Analog 81	$-(CH_2)_3NHC(O)NHCH(CH_3)_2$	$-CH_3$	3.33	10	1134	490	1

Analog 82	-$(CH_2)_3NHC(O)NHCH(CH_3)_2$	-$CH_2CH_2CH_3$	0.12	1.11	6571	3740	2
Analog 83	-$(CH_2)_3NHC(O)NHCH(CH_3)_2$	-$(CH_2)_2OCH_3$	0.12	1.11	1289	1259	1
Example 120	-$(CH_2)_3NH_2$	-$(CH_2)_2OH$	3.33	>30	5636	*	1
Analog 84	-$(CH_2)_3NH_2$	-CH_3	3.33	>30	421	*	1
Analog 85	-$(CH_2)_3NH_2$	-$CH_2OCH_2CH_3$	0.12	30	1325	411	1
Analog 86	-$(CH_2)_3NH_2$	-$(CH_2)_2OCH_3$	0.04	1.11	3433	1674	1
Example 128	-$(CH_2)_3NHC(O)$- 	-$(CH_2)_2OH$	30	>30	75	*	3
Analog 87	-$(CH_2)_3NHC(O)$- 	-CH_3	0.37	30	4843	463	2
Analog 88	-$(CH_2)_3NHC(O)$- 	-$CH_2OCH_2CH_3$	0.12	1.11	6670	1379	2
Analog 89	-$(CH_2)_3NHC(O)$- 	-$(CH_2)_2OCH_3$	0.014	0.014	5915	6169	2
Example 130	-$CH_2C(CH_3)_2CH_2NHC(O)NH$- 	-$(CH_2)_2OH$	0.014	3.33	8361	2001	1
Analog 90	-$CH_2C(CH_3)_2CH_2NHC(O)NH$- 	-CH_2CH_3	0.014	0.12	922	2098	2
Analog 91	-$CH_2C(CH_3)_2CH_2NHC(O)NH$- 	-$CH_2OCH_2CH_3$	0.014	0.04	1133	3618	2
Analog 92	-$CH_2C(CH_3)_2CH_2NHC(O)NH$- 	-$(CH_2)_2OCH_3$	0.014	0.04	570	6449	2

Example 5	-CH$_2$C(CH$_3$)$_2$NHC(O)– 	-CH$_2$OH	0.37	10	17274	1130	1
Analog 93	-CH$_2$C(CH$_3$)$_2$NHC(O)– 	-CH$_2$OCH$_2$CH$_3$	0.37	0.37	1052	12173	13
Analog 94	-CH$_2$C(CH$_3$)$_2$NHC(O)– 	-CH$_2$OCH$_3$	1.11	3.33	2518	9721	1
Example 124	-CH$_2$C(CH$_3$)$_2$CH$_2$NHC(O)– 	-(CH$_2$)$_2$OH	0.12	3.33	3980	1446	1
Analog 95	-CH$_2$C(CH$_3$)$_2$CH$_2$NHC(O)– 	-CH$_2$OCH$_2$CH$_3$	0.04	0.37	832	1820	5
Analog 96	-CH$_2$C(CH$_3$)$_2$CH$_2$NHC(O)– 	-(CH$_2$)$_2$OCH$_3$	0.014	0.014	2133	1812	1
Example 126	-(CH$_2$)$_3$NHC(O)NH(CH$_2$)$_3$CH$_3$	-(CH$_2$)$_2$OH	1.11	>30	8361	*	1
Analog 97	-(CH$_2$)$_3$NHC(O)NH(CH$_2$)$_3$CH$_3$	-CH$_2$OCH$_2$CH$_3$	0.37	3.33	827	963	5
Analog 98	-(CH$_2$)$_3$NHC(O)NH(CH$_2$)$_3$CH$_3$	-(CH$_2$)$_2$OCH$_3$	0.014	0.04	5915	6169	2
Example 129	-CH$_2$C(CH$_3$)$_2$CH$_2$NH$_2$	-(CH$_2$)$_2$OH	0.37	30	2702	85	1
Analog 99	-CH$_2$C(CH$_3$)$_2$CH$_2$NH$_2$	-CH$_2$CH$_3$	0.04	0.37	405	13846	1
Analog 100	-CH$_2$C(CH$_3$)$_2$CH$_2$NH$_2$	-(CH$_2$)$_2$OCH$_3$	0.014	0.04	571	17626	1
Example 132	-(CH$_2$)$_3$NHC(O)– 	-(CH$_2$)$_2$OH	0.37	>30	8361	*	1
Analog 101	-(CH$_2$)$_3$NHC(O)– 	-CH$_3$	1.11	3.33	571	156	3

Analog 102	$-(CH_2)_3NHC(O)-$ 	$-(CH_2)_2OCH_3$	0.014	1.11	1504	3080	2
Example 137	$-(CH_2)_2NHC(O)NHCH_2CH_3$	$-(CH_2)_2OH$	30	30	801	73	1
Analog 103	$-(CH_2)_2NHC(O)NHCH_2CH_3$	$-CH_2CH_3$	3.33	10	1031	3250	2
Analog 104	$-(CH_2)_2NHC(O)NHCH_2CH_3$	$-(CH_2)_2OCH_3$	0.014	0.12	2587	7719	4
Example 138	$-(CH_2)_2NHC(O)CH_2CH(CH_3)_2$	$-(CH_2)_2OH$	3.33	>30	36	*	1
Analog 105	$-(CH_2)_2NHC(O)CH_2CH(CH_3)_2$	$-CH_2CH_3$	3.33	30	851	587	2
Analog 106	$-(CH_2)_2NHC(O)CH_2CH(CH_3)_2$	$-(CH_2)_2OCH_3$	0.12	3.33	1204	5694	5
Example 142	$-CH_2C(CH_3)_2NHC(O)NHCH(CH_3)_2$	$-CH_2OH$	1.11	>30	1554	*	1
Analog 107	$-CH_2C(CH_3)_2NHC(O)NHCH(CH_3)_2$	$-CH_2CH_2CH_3$	1.11	3.33	1428	6363	3
Analog 108	$-CH_2C(CH_3)_2NHC(O)NHCH(CH_3)_2$	$-CH_2OCH_2CH_3$	0.37	1.11	966	10587	4
Example 1	$-(CH_2)_3NHS(O)_2-$ 	$-(CH_2)_2OH$	0.37	10	1072	143	1
Analog 109	$-(CH_2)_3NHS(O)_2-$ 	$-(CH_2)_2OCH_3$	0.04	0.37	638	6169	2
Example 2	$-(CH_2)_3NHC(O)-$ 	$-(CH_2)_2OH$	3.33	3.33	507	45	1
Analog 110	$-(CH_2)_3NHC(O)-$ 	$-(CH_2)_2OCH_3$	0.12	1.11	647	6169	2
Example 4	$-CH_2C(CH_3)_2NH_2$	$-CH_2OH$	0.37	3.33	1893	41	2
Analog 111	$-CH_2C(CH_3)_2NH_2$	$-CH_2OCH_2CH_3$	0.12	0.37	656	11475	7

Example 111	-$(CH_2)_4$NHC(O)- 	-$(CH_2)_2$OH	0.12	1.11	7753	983	1
Analog 112	-$(CH_2)_4$NHC(O)- 	-$(CH_2)_2OCH_3$	0.014	0.04	2127	1462	7
Example 112	-$(CH_2)_4$NHS$(O)_2$- 	-$(CH_2)_2$OH	1.11	30	8361	76	1
Analog 113	-$(CH_2)_4$NHS$(O)_2$- 	-$(CH_2)_2OCH_3$	0.014	0.04	6032	3786	4
Example 114	-$(CH_2)_4NH_2$	-$(CH_2)_2$OH	30	>30	23	*	1
Analog 114	-$(CH_2)_4NH_2$	-$(CH_2)_2OCH_3$	0.04	0.37	127231	724	1
Example 116	-$(CH_2)_4$NHC(O)- 	-$(CH_2)_2$OH	0.37	30	8361	1112	1
Analog 115	-$(CH_2)_4$NHC(O)- 	-$(CH_2)_2OCH_3$	0.014	0.04	7545	9340	2
Example 117	-$(CH_2)_4$NHC(O)- 	-$(CH_2)_2$OH	0.37	3.33	5520	1938	1
Analog 116	-$(CH_2)_4$NHC(O)- 	-$(CH_2)_2OCH_3$	0.014	0.04	1129	7261	3

Example 118	-$(CH_2)_8NHC(O)NH$- 	-$(CH_2)_2OH$	0.37	>30	5177	*	1
Analog 117	-$(CH_2)_8NHC(O)NH$- 	-$(CH_2)_2OCH_3$	0.014	0.12	1257	1372	1
Example 119	-$(CH_2)_8NHS(O)_2CH_3$	-$(CH_2)_2OH$	0.04	3.33	8361	693	1
Analog 118	-$(CH_2)_8NHS(O)_2CH_3$	-$(CH_2)_2OCH_3$	0.014	0.014	1914	1853	2
Example 121	-$(CH_2)_8NHC(O)$- 	-$(CH_2)_2OH$	0.37	3.33	2441	180	1
Analog 119	-$(CH_2)_8NHC(O)$- 	-$(CH_2)_2OCH_3$	0.014	0.014	1584	1995	1
Example 134	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$- 	-$(CH_2)_2OH$	3.33	30	8361	315	1
Analog 120	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$- 	-$(CH_2)_2OCH_3$	0.04	0.37	1394	3317	1
Example 135	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$- 	-$(CH_2)_2OH$	3.33	30	2464	146	1
Analog 121	-$(CH_2)_2O(CH_2)_2N(CH_3)C(O)$- 	-$(CH_2)_2OCH_3$	0.37	1.11	1234	4849	2
Example 140	-$(CH_2)_2O(CH_2)_2NHC(O)(CH_2)_{14}CH_3$	-$(CH_2)_2OH$	1.11	>30	673	*	1
Analog 121	-$(CH_2)_2O(CH_2)_2NHC(O)(CH_2)_{14}CH_3$	-$(CH_2)_2OCH_3$	0.014	0.014	2556	11033	9
Example 141	-$(CH_2)_3NHC(O)CH(CH_3)_2$	-$(CH_2)_2OH$	0.04	30	14046	243	1
Analog 123	-$(CH_2)_3NHC(O)CH(CH_3)_2$	-CH_3	1.11	10	3011	405	2
Example 364	-$CH_2C(CH_3)_2CH_2S(O)_2CH_3$	-CH_2OH	1.11	30	5343	164	1

Analog 124	$-CH_2C(CH_3)_2CH_2S(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.12	0.37	1924	9513	4
Example 365	$-(CH_2)_2NHC(O)NHCH(CH_3)_2$	$-CH_2OH$	0.37	3.33	1488	74	1
Analog 125	$-(CH_2)_2NHC(O)NHCH(CH_3)_2$	$-CH_2OCH_2CH_3$	0.37	10	2045	7512	7

*TNF below experimental background of 40 pg/mL

Analogs 1-5, 47-52, 58-74, 109, 113, and 118 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,331,539 and 6,677,349.

Analogs 53-57, 81-83, 87-91, 97, 98, 103, 104, 107, and 108 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,541,485 and 6,573,273.

Analogs 73-76 and 124 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent No. 6,664,264.

Analogs 77-80 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent No. 6,683,088.

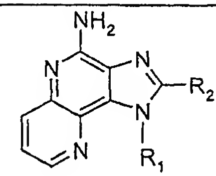
Analogs 84-86, 99, 100, 111, and 114 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,069,149 and 6,677,349.

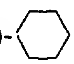
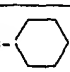
Analogs 93-96, 101, 102, 105, 106, 110, 112, 115, 116, 119, and 123 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent Nos. 6,451,810 and 6,756,382.

Analogs 120-122 are either specifically exemplified in or are readily prepared using the synthetic methods disclosed in U.S. Patent No. 6,664,265.

Compounds of the invention and in some instances, close analogs (Table 13 below), were tested for their ability to induce cytokine biosynthesis using the test method described above. The minimum effective concentration for the induction of IFN-α, minimum effective concentration for the induction of TNF-α, the maximal response for IFN-α, and the maximal response for TNF-α are shown in Table 12 below where # is the number of separate experiments in which the compound was tested. When a compound was tested in more than one experiment the values shown are the median values.

Table 12



Compound	R_1	R_2	Minimum Effective Concentration (µM)		Maximal Response (pg/mL)		#
			IFN	TNF	IFN	TNF	
Example 148	$-CH_2C(CH_3)_2OH$	$-CH_2OH$	1.11	10	2290	1316	3
Example 149	$-CH_2C(CH_3)_2OH$	$-(CH_2)_2OH$	3.33	30	2063	331	2
Analog 6	$-CH_2C(CH_3)_2OH$	$-CH_2OCH_2CH_3$	0.12	1.11	1674	7275	2
Analog 7	$-CH_2C(CH_3)_2OH$	$-(CH_2)_2OCH_3$	0.04	0.37	3142	7503	2
Analog 126	$-CH_2C(CH_3)_2OH$	$-CH_3$	0.37	3.33	1952	6519	1
Analog 127	$-CH_2C(CH_3)_2OH$	$-CH_2CH_3$	0.37	3.33	2150	3863	1
Analog 128	$-CH_2C(CH_3)_2OH$	$-CH_2CH_2CH_3$	0.12	1.11	2484	5526	1
Example 143	$-CH_2C(CH)_3NH(CO)-$ 	$-CH_2OH$	1.11	10	1467	798	1
Analog 129	$-CH_2C(CH)_3NH(CO)-$ 	$-CH_2OCH_2CH_3$	0.014	0.014	1647	8691	1
Example 144	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OH$	10	30	1914	170	1
Analog 130	$-CH_2C(CH_3)_2NHS(O)_2CH_3$	$-CH_2OCH_2CH_3$	0.04	0.37	2465	9234	1
Example 551	$-CH_2CF(CH_3)_2$	$-CH_2OH$	1.11	3.33	1833	1922	1

Example 552	$-CH_2CF(CH_3)_2$	$-(CH_2)_2OH$	1.11	10	1646	84	1
Analog 131	$-CH_2CF(CH_3)_2$	$-CH_3$	0.37	10	2120	1679	2
Example 633	$-CH_2CH(CH_3)_2$	$-CH_2OH$	1.11	30	1592	363	1
Analog 132	$-CH_2CH(CH_3)_2$	$-CH_2OCH_2CH_3$	0.12	1.11	1524	3160	2
Analog 133	$-CH_2CH(CH_3)_2$	$-CH_3$	0.37	1.11	1117	699	12
Example 145	$-(CH_2)_4NHS(O)_2CH_3$	$-(CH_2)_2OH$	1.11	30	3008	7	2
Example 146	$-(CH_2)_2NHS(O)_2CH_3$	$-CH_2OH$	10	>30	1520	*	1
Example 147	$-(CH_2)_2NHS(O)_2CH_3$	$-(CH_2)_2OH$	30	>30	49	*	1

*Below the experimental background of 40 pg/mL

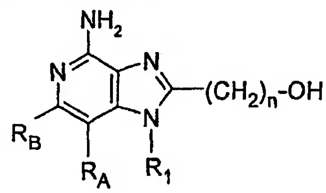
Table 13		
Analog	Chemical Name	Reference
6	1-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol	Example 148 Part E
7	1-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]-2-methylpropan-2-ol	Example 149 Part J
126	1-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol	U.S. Patent No. 6,194,425**
127	1-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol	U.S. Patent No. 6,194,425**
128	1-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-2-methylpropan-2-ol	U.S. Patent No. 6,194,425**
129	*N*-[2-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide	Example 143 Part H
130	*N*-[2-(4-amino-2-ethoxoxymethyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)-1,1-dimethylethyl]methanesulfonamide	Example 144 Part A
131	1-(2-fluoro-2-methylpropyl)-2-methyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. Patent No. 6,194,425**
132	2-ethoxymethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. Patent No. 6,194,425**
133	2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine	U.S. Patent No. 6,194,425 Example 36

**Although not a working example, the compound is readily prepared using the disclosed synthetic methods.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of Formula I:



I

wherein:

n is 1 or 2;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted at a carbon atom by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

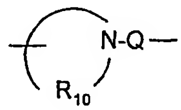
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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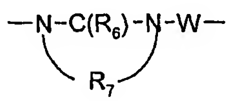

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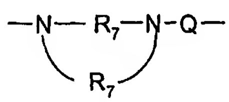

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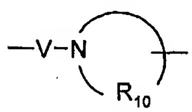

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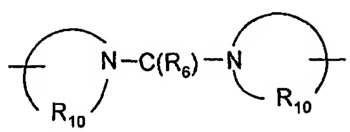
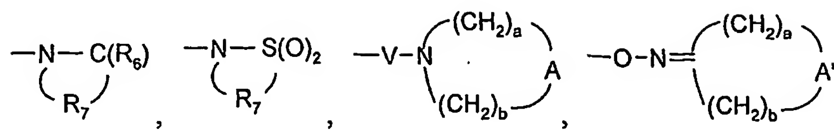


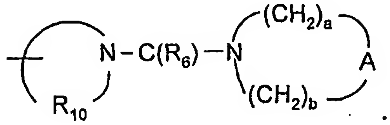
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

, and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

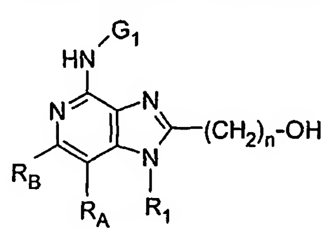
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof to the animal.

2. A method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of Formula II:



II

wherein:

G_1 is selected from the group consisting of:

-C(O)-R',

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

-C(O)-O-R',

-C(O)-N(R")R',

-C(=NY')-R',

-CH(OH)-C(O)-OY',

-CH(OC$_{1-4}$ alkyl)Y$_0$,

-CH$_2$Y$_1$, and

-CH(CH$_3$)Y$_1$;

R' and R" are independently selected from the group consisting of C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, aryl, heteroaryl, aryl-C$_{1-4}$ alkylenyl, heteroaryl-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkylenyl, halo-C$_{1-4}$ alkoxy, -O-C(O)-CH$_3$, -C(O)-O-CH$_3$, -C(O)-NH$_2$, -O-CH$_2$-C(O)-NH$_2$, -NH$_2$, and –S(O)$_2$-NH$_2$, with the proviso that R" can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

Y' is selected from the group consisting of hydrogen, C$_{1-6}$ alkyl, and benzyl;

Y$_0$ is selected from the group consisting of C$_{1-6}$ alkyl, carboxy-C$_{1-6}$ alkylenyl, amino-C$_{1-4}$ alkylenyl, mono-*N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl, and di-*N,N*-C$_{1-6}$ alkylamino-C$_{1-4}$ alkylenyl;

Y$_1$ is selected from the group consisting of mono-*N*-C$_{1-6}$ alkylamino, di-*N,N*-C$_{1-6}$ alkylamino, morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, and 4-C$_{1-4}$ alkylpiperazin-1-yl;

n is 1 or 2;

R$_A$ and R$_B$ are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

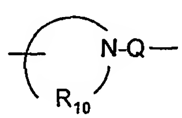
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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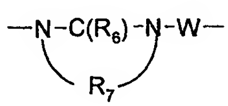

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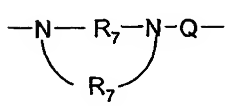

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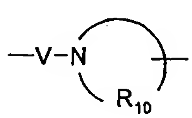

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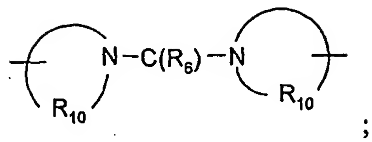
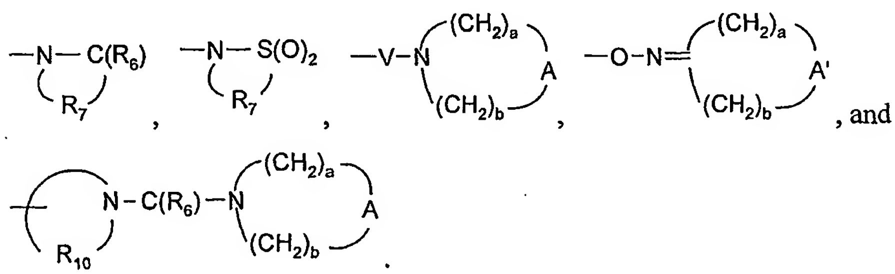


Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(Q-R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

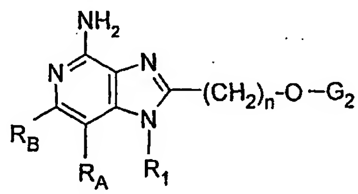
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof to the animal.

3. A method of preferentially inducing the biosynthesis of IFN-α in an animal comprising administering an effective amount of a compound of Formula III:



III

wherein:

G_2 is selected from the group consisting of:

$-X_2-C(O)-R'$,

α-aminoacyl,

α-aminoacyl-α-aminoacyl,

$-X_2-C(O)-O-R'$, and

$-C(O)-N(R'')R'$;

X_2 is selected from the group consisting of a bond; $-CH_2-O-$; $-CH(CH_3)-O-$; $-C(CH_3)_2-O-$; and, in the case of $-X_2-C(O)-O-R'$, $-CH_2-NH-$;

R' and R'' are independently selected from the group consisting of C_{1-10} alkyl, C_{3-7} cycloalkyl, phenyl, benzyl, and 2-phenylethyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of halogen, hydroxy, nitro, cyano, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, aryl, heteroaryl, aryl-C_{1-4} alkylenyl, heteroaryl-C_{1-4} alkylenyl, halo-C_{1-4} alkylenyl, halo-C_{1-4} alkoxy, $-O-C(O)-CH_3$, $-C(O)-O-CH_3$, $-C(O)-NH_2$, $-O-CH_2-C(O)-NH_2$, $-NH_2$, and $-S(O)_2-NH_2$, with the proviso that R'' can also be hydrogen;

α-aminoacyl is an α-aminoacyl group derived from an α-amino acid selected from the group consisting of racemic, D-, and L-amino acids;

n is 1 or 2;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

-X-R_5;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X-R_4,

-Z-X-Y-R_4,

-Z-X-Y-X-Y-R_4, and

-Z-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

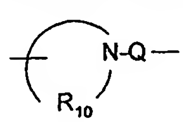
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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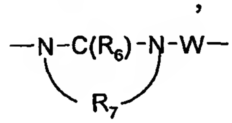

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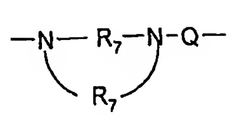
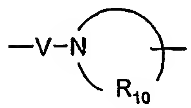
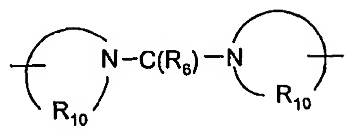
,

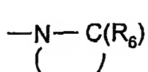
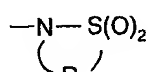
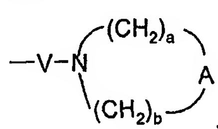
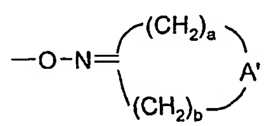
, and

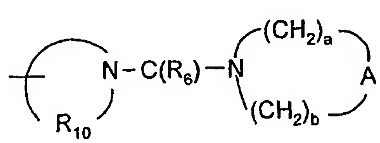
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -CH$_2$-, -S(O)$_{0-2}$-, and -N(Q-R$_4$)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R$_4$)-, and -CH$_2$-;

Q is selected from the group consisting of a bond, -C(R$_6$)-, -C(R$_6$)-C(R$_6$)-, -S(O)$_2$-, -C(R$_6$)-N(R$_8$)-W-, -S(O)$_2$-N(R$_8$)-, -C(R$_6$)-O-, -C(R$_6$)-S-, and -C(R$_6$)-N(OR$_9$)-;

V is selected from the group consisting of -C(R$_6$)-, -O-C(R$_6$)-, -N(R$_8$)-C(R$_6$)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof to the animal.

4. The method of any one of claims 1, 2 and 3, wherein n is 1.

5. The method of any one of claims 1, 2, and 3, wherein n is 2.

6. The method of any one of claims 1 through 5 wherein R_A and R_B form a fused benzene ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

7. The method of any one of claims 1 through 5 wherein R_A and R_B form a fused pyridine ring which is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

8. The method of any one of claims 1 through 5 wherein R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted or substituted by one or more R groups.

9. The method of any one of claims 1 through 5 wherein R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and -N(R$_9$)$_2$.

10. The method of claim 9 wherein R_A and R_B are each methyl.

11. The method of any one of claims 1 through 10 wherein R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X^1-Y^1-R_4, and

-X-R_5; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of:

-O-,

-$S(O)_2$-,

-$S(O)_2$-N(R_8)-,

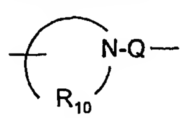
-C(O)-,

-C(O)-O-,

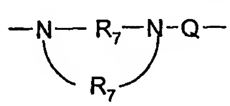
-O-C(O)-,

-N(R_8)-Q-,

-C(O)-N(R_8)-,



, and



;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

-S-,

-C(O)-,

-C(O)-O-,

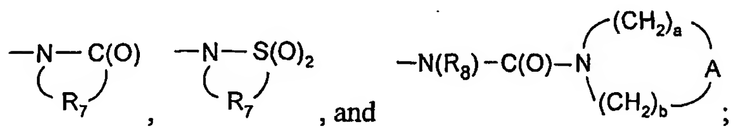
-C(O)-N(R_8)-,

-S(O)$_2$-N(R$_8$)-, and

-N(R$_8$)-C(O)-;

R$_4$ is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R$_5$ is selected from the group consisting of:



R$_6$ is selected from the group consisting of =O and =S;

R$_7$ is C$_{2-7}$ alkylene;

R$_8$ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R$_{10}$ is C$_{3-8}$ alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R$_4$)-;

Q is selected from the group consisting of a bond, -C(R$_6$)-, -S(O)$_2$-, -C(R$_6$)-N(R$_8$)-W-, -S(O)$_2$-N(R$_8$)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7.

12. The method of any one of claims 1 through 11 wherein R$_1$ is selected from the group consisting of C$_{1-5}$ alkyl, C$_{2-5}$ alkynyl, arylC$_{1-4}$ alkylenyl, cycloalkylC$_{1-4}$ alkylenyl, C$_{1-4}$ alkyl-S(O)$_2$-C$_{1-4}$ alkylenyl, aryl-S(O)$_2$-C$_{1-4}$ alkylenyl, C$_{1-4}$ alkyl-S(O)$_2$-C$_{1-4}$ alkylenyl-O-C$_{1-4}$ alkylenyl, C$_{1-4}$ alkyl-S(O)$_2$-NH-C$_{1-4}$ alkylenyl, hydroxyC$_{1-4}$ alkylenyl, dihydroxyC$_{1-4}$alkylenyl, haloC$_{1-4}$ alkylenyl, aminoC$_{1-4}$ alkylenyl, C$_{1-4}$ alkyl-C(O)-O-C$_{1-4}$ alkylenyl, C$_{1-6}$ alkyl-C(O)-NH-C$_{1-4}$ alkylenyl, aryl-C(O)-NH-C$_{1-4}$ alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C$_{1-4}$ alkylenyl,

di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one, two, or three substituents selected from the group consisting of alkyl, aryl, heteroaryl, and oxo.

13. The method of any one of claims 1 through 12 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 2-fluoro-2-methylpropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-(methylsulfonyl)ethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 2,2-dimethyl-3-(methylsulfonyl)propyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-{[(1-methylethyl)sulfonyl]amino}ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-methyl-2-[(ethylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-({[(1-methylethyl)amino]carbonyl}amino)propyl,

2-({[(1-methylethyl)amino]carbonyl}amino)ethyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, tetrahydro-2*H*-pyran-4-ylmethyl, 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

14. The method of any one of claims 1 through 11 wherein R_1 is selected from the group consisting of alkyl, aminoalkyl, dihydroxyalkyl, haloalkyl, and hydroxyalkyl.

15. The method of claim 14 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2-amino-2-methylpropyl, 3-amino-2,2-dimethylpropyl, 2,3-dihydroxypropyl, 2-fluoro-2-methylpropyl, and 2-hydroxy-2-methylpropyl.

16. The compound or salt of claim 14 wherein R_1 is selected from the group consisting of (1-hydroxycyclobutyl)methyl, (1-hydroxycyclopentyl)methyl, and (1-hydroxycyclohexyl)methyl.

17. The method of any one of claims 1 through 11 wherein R_1 is heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, aryl, heteroaryl, hydroxy, and oxo.

18. The method of claim 17 wherein heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and morpholinyl, each of which is unsubstituted or substituted by one, two, or three substituents selected from the group consisting of alkyl, aryl, heteroaryl, and oxo.

19. The method of claim 18 wherein heterocyclyl is selected from the group consisting of 1,3-dioxolanyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, and

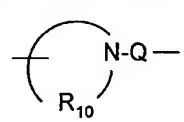
morpholinyl, each of which is unsubstituted or substituted by one, two, or three substituents selected from the group consisting of alkyl, aryl, heteroaryl, and oxo; and alkylenyl is C_{1-4} alkylenyl.

20. The method of claim 19 wherein R_1 is selected from the group consisting of tetrahydro-2*H*-pyran-4-ylmethyl and (2,2-dimethyl-1,3-dioxolan-4-yl)methyl.

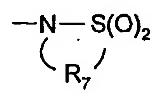
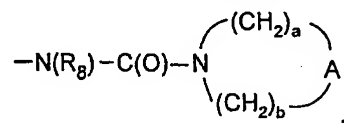
21. The compound or salt of claim 17 wherein R_1 is (4-hydroxytetrahydro-2*H*-pyran-4-yl)methyl.

22. The method of any one of claims 1 through 11 wherein R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by one -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, and -S(O)$_2$ wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

23. The method of claim 22 wherein R_1 is selected from the group consisting of 2-[(cyclopropylcarbonyl)amino]ethyl, 4-[(cyclopropylcarbonyl)amino]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(1-methylethyl)carbonyl]amino}ethyl, 4-{[(1-methylethyl)carbonyl]amino}butyl, 2-methyl-2-{[(1-methylethyl)carbonyl]amino}propyl, 2-[(methylsulfonyl)amino]ethyl, 4-[(methylsulfonyl)amino]butyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, and 2,2-dimethyl-3-(methylsulfonyl)propyl.

24. The method of any one of claims 1 through 11 wherein R_1 is -X-Y-R_4 wherein X is C_{1-6} alkylene which may be interrupted by an -O- group; Y is selected from the group consisting of -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, -S(O)$_2$-, and  wherein Q is -C(O)-, -C(O)-NH-, or

$-S(O)_2-$, R_{10} is pentylene, R_8 is hydrogen or methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, hydroxyC_{1-6} alkyl, isoquinolinyl, *N*-methylimidazolyl, pyridinyl, quinolinyl, benzyl, 1-phenylethyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of chloro, cyano, fluoro, hydroxy, and methyl.

25. The method of any one of claims 1 through 11 wherein R_1 is -X-R_5 wherein X is C_{1-6} alkylene, and R_5 is  or  .

26. The method of claim 25 wherein R_1 is selected from the group consisting of 4-(1,1-dioxidoisothiazolidin-2-yl)butyl, 4-[(4-morpholinecarbonyl)amino]butyl, and 2-[(4-morpholinecarbonyl)amino]ethyl.

27. The method of any one of claims 1 through 7 or 11 through 26 except as dependent on claim 8, 9, or 10 wherein R_3 is selected from the group consisting of aryl, arylalkyleneoxy, heteroaryl, and heteroarylalkyleneoxy, wherein aryl, arylalkyleneoxy, heteroaryl, and heteroarylalkyleneoxy, are unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

28. The method of claim 27 wherein R_3 is phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, quinolin-3-yl, or thiazol-4-ylmethoxy any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

29. The method of claim 28 wherein R_3 is selected from the group consisting of pyridin-3-yl, pyridin-4-yl, 6-fluoropyridin-3-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, quinolin-3-yl, and thiazol-4-ylmethoxy.

30. The compound or salt of any one of claims 1 through 7 or 11 through 26 except as dependent on claim 8, 9, or 10 wherein R_3 is thien-3-yl, phenyl, pyridin-2-yl, pyridin-3-yl,

pyridin-4-yl, or quinolin-3-yl any of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halogen, cyano, hydroxy, and hydroxyalkyl.

31. The method of any one of claims 1 through 7, or 11 through 26 except as dependent on claim 8, 9, or 10 wherein R_3 is -Z-X-Y-R_4 wherein X is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; Z is a bond; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl.

32. The method of any one of claims 1 through 7, or 11 through 26 except as dependent on claim 8, 9, or 10 wherein R_3 is -Z-X-Y-R_4 wherein Z is a bond, X is phenylene, Y is selected from the group consisting of -C(O)-, -C(O)-N(R_8)-, -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, and -N(R_8)-C(O)-N(R_8)- wherein R_8 is selected from hydrogen and methyl; and R_4 is selected from the group consisting of C_{1-6} alkyl, phenyl, and phenyl substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen, hydroxy, and hydroxyalkyl; with the proviso that when Y is -C(O)-N(R_8)- or -N(R_8)-C(O)-N(R_8)- then R_4 can also be hydrogen; and with the further proviso that when Y is -C(O)- or -N(R_8)-C(O)- then R_4 can also be morpholin-4-yl, piperidin-1-yl, or pyrrolidin-1-yl.

33. The method of claim 32 wherein R_3 is 3-(methylsulfonylamino)phenyl, 3-(pyrrolidin-1-ylcarbonyl)phenyl, or 3-(morpholin-4-ylcarbonyl)phenyl.

34. The method of any one of claims 1 through 8, or 11 through 33 except as dependent on claim 9 or 10 wherein R is not present.

35. The method of any one of claims 1 through 7, or 11 through 26 except as dependent on claim 8, 9, or 10 wherein neither R_3 nor R is present.

36. The method of any one of claims 1 through 8, or 11 through 26 except as dependent on claim 9 or 10 wherein R is selected from the group consisting of hydroxy and methoxy.

37. The method of claim 36 as dependent on any one of claims 1 through 7, or 11 through 26 except as dependent on claim 8, 9, or 10 wherein R_3 is not present.

38. The method of any one of claims 1 through 37 wherein an effective amount of the compound or salt is administered as a pharmaceutical composition comprising a therapeutically effective amount of the compound or salt and a pharmaceutically acceptable carrier.

39. A method of treating a viral disease in an animal in need thereof comprising preferentially inducing the biosynthesis of IFN-α in the animal according to the method of any one of claims 1 through 38.

40. A method of treating a neoplastic disease in an animal in need thereof comprising preferentially inducing the biosynthesis of IFN-α in the animal according to the method of any one of claims 1 through 38.

41. The method of anyone of claims 1 through 40 wherein the compound or salt is administered systemically.

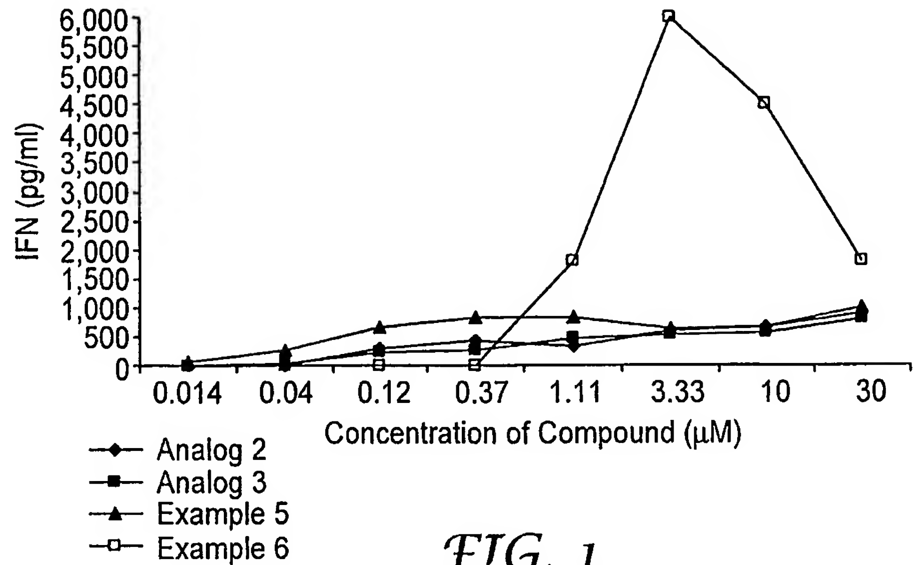

6,000
5,500
5,000
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
IFN (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (µM)
Analog 2
Analog 3
Example 5
Example 6

FIG. 1

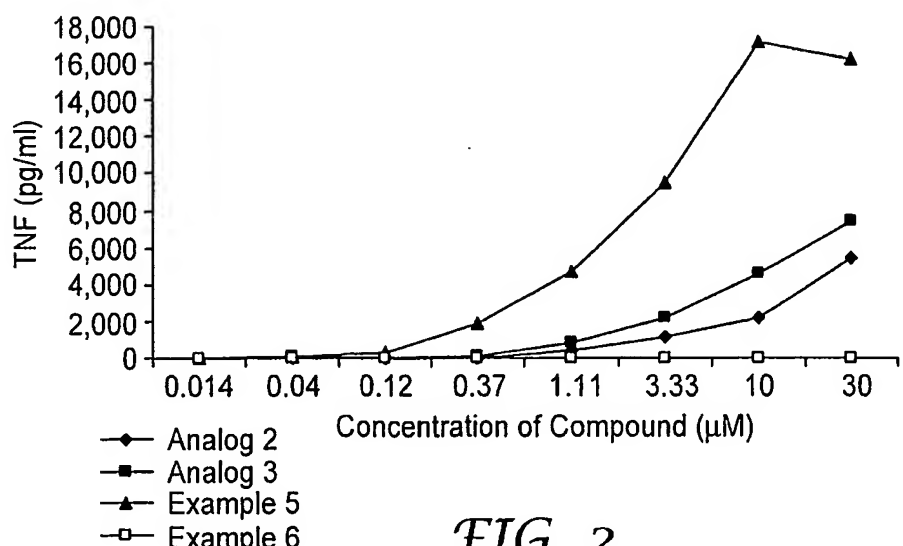

18,000
16,000
14,000
12,000
10,000
8,000
6,000
4,000
2,000
0
TNF (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (µM)
Analog 2
Analog 3
Example 5
Example 6

FIG. 2

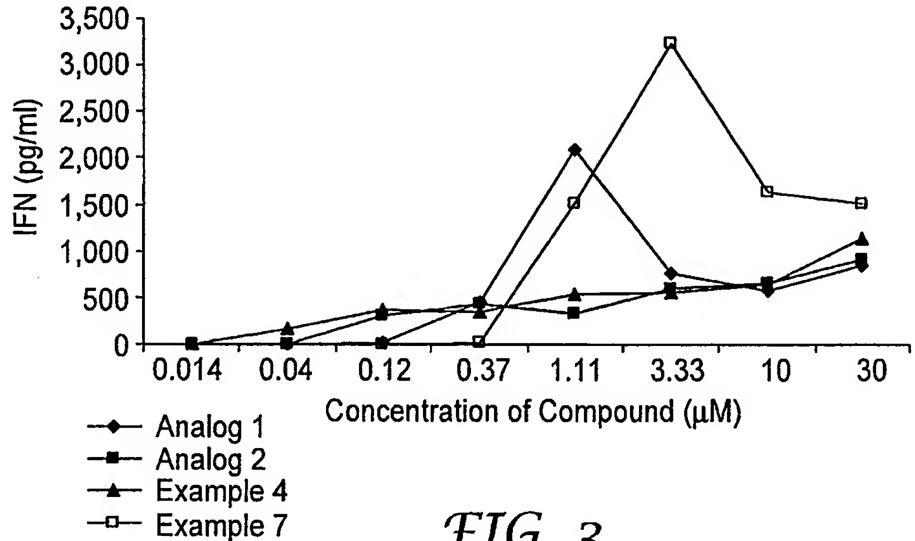

3,500
3,000
2,500
2,000
1,500
1,000
500
0
IFN (pg/ml)
0.014 0.04 0.12 0.37 1.11 3.33 10 30
Concentration of Compound (µM)
Analog 1
Analog 2
Example 4
Example 7

FIG. 3

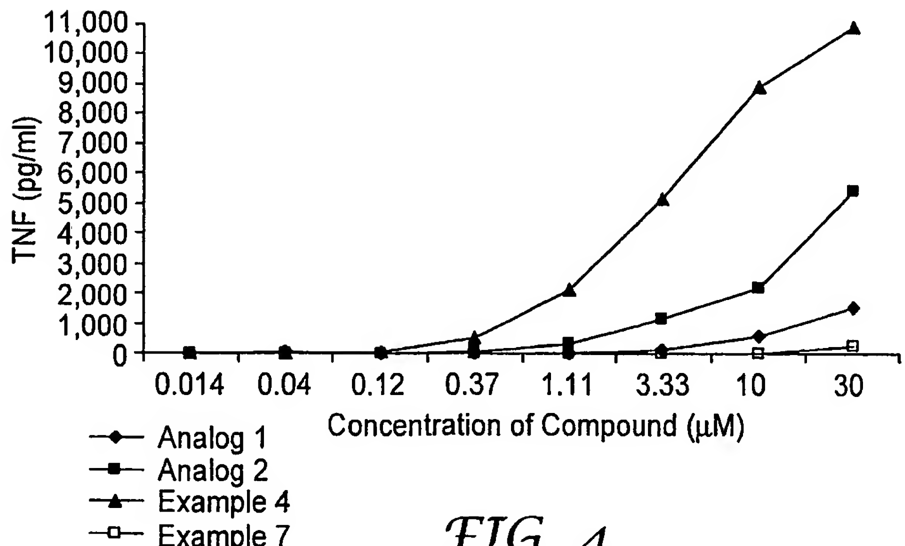

11,000
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
TNF (pg/ml)
0.014 0.04 0.12 0.37 1.11 3.33 10 30
Concentration of Compound (µM)
Analog 1
Analog 2
Example 4
Example 7

FIG. 4

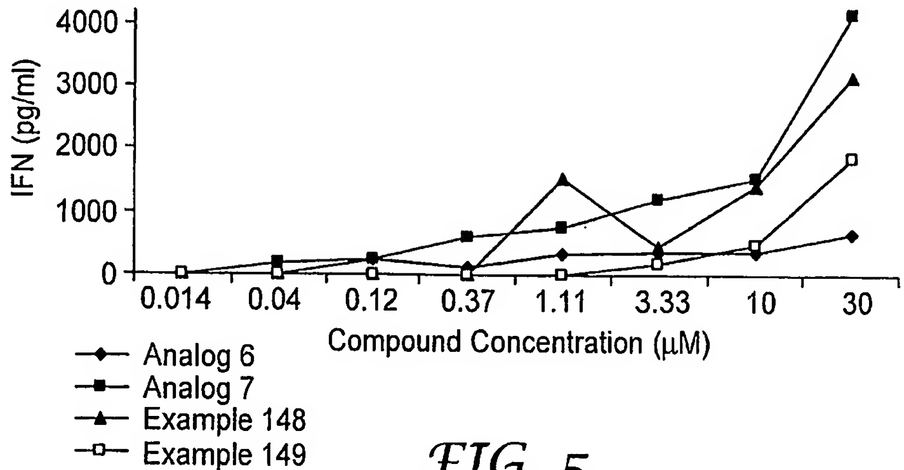

4000
3000
2000
1000
0
IFN (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Compound Concentration (μM)
Analog 6
Analog 7
Example 148
Example 149

FIG. 5

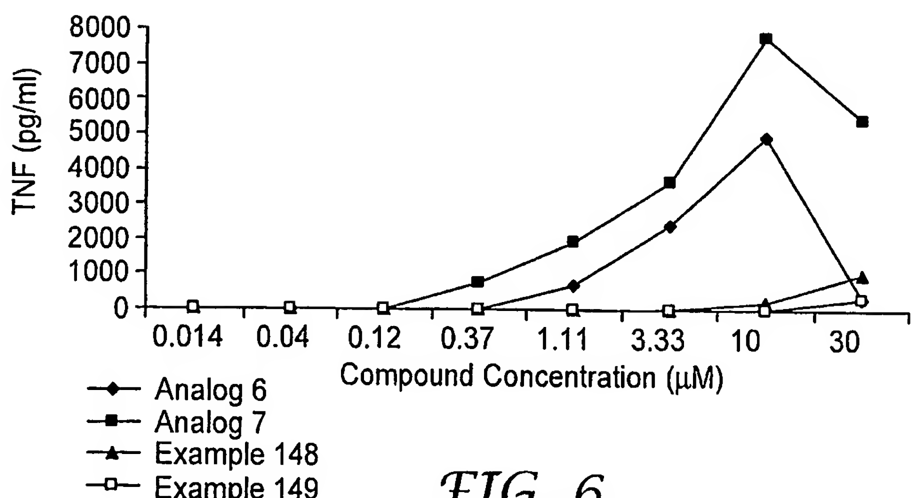

8000
7000
6000
5000
4000
3000
2000
1000
0
TNF (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Compound Concentration (μM)
Analog 6
Analog 7
Example 148
Example 149

FIG. 6

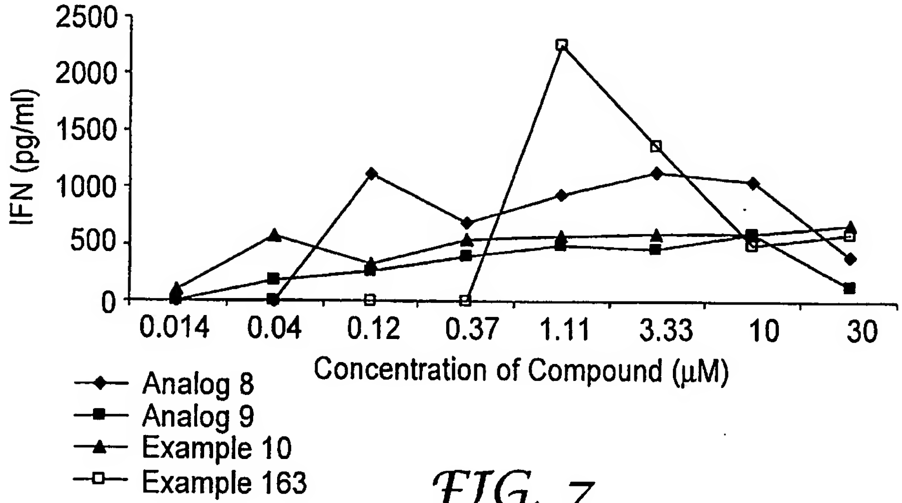

2500
2000
1500
1000
500
0
IFN (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 8
Analog 9
Example 10
Example 163

FIG. 7

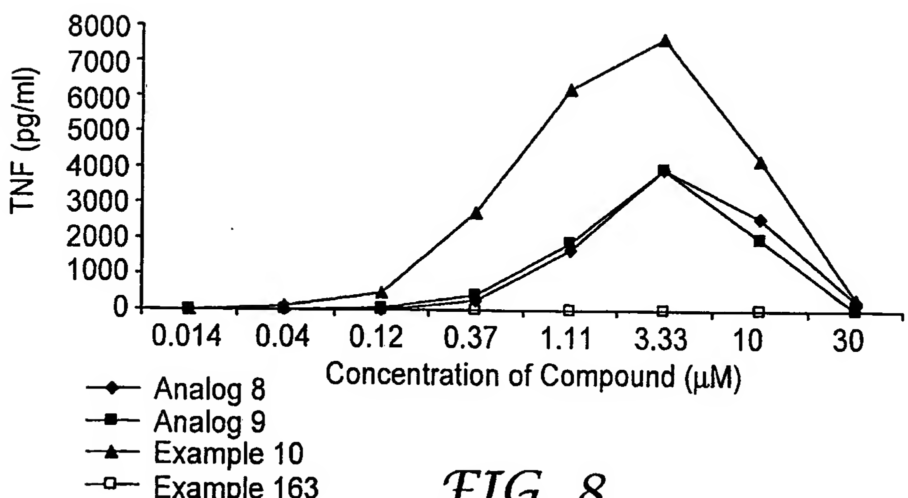

8000
7000
6000
5000
4000
3000
2000
1000
0
TNF (pg/ml)
0.014
0.04
0.12
0.37
1.11
3.33
10
30
Concentration of Compound (μM)
Analog 8
Analog 9
Example 10
Example 163

FIG. 8